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(54) Title: MUSCARINIC RECEPTOR ANTAGONISTS

(57) Abstract

Disclosed are multibinding compounds which are muscarinic receptor antagonists. The multibinding compounds of this invention containing from 2 to 10 ligands covalently attached to one or more linkers. Each ligand is, independently of each other, a muscarinic receptor antagonist or an allosteric modulator provided that at least one of said ligand is a muscarinic receptor antagonist. The multibinding compounds of this invention are useful in the treatment and prevention of diseases such as chronic obstructive pulmonary disease, chronic bronchitis, irritable bowel syndrome, urinary incontinence, and the like.

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MUSCARINIC RECEPTOR ANTAGONISTS

BACKGROUND OF THE INVENTION

CROSS-REFERENCE TO RELATED APPLICATIONS:

This application claims the benefit of U.S. Patent Application Serial No. 60/088,466, filed June 8, 1998; U.S. Patent Application Serial No. 60/092,938, filed July 15, 1998; and U.S. Patent Application Serial No. 60/120,287, filed February 16, 1999; the disclosures of which are incorporated herein by reference in their entirety.

Field of the Invention

This invention relates to novel multibinding compounds (agents) that are muscarinic receptor antagonsits, pharmaceutical compositions comprising such compounds, and methods of preparing these compounds. Accordingly, the multibinding compounds and pharmaceutical compositions of this invention are useful in the treatment and prevention of diseases mediated by these receptors such as chronic obstructive pulmonary disease, chronic bronchitis, irritable bowel syndrome, urinary incontinence, and the like.

References

The following publications are cited in this application as superscript numbers:

[1] Bonner, T. I. et al., *Science* (Washington D.C.) **1987**, *237*, 527-532.

[2] Goyal, R. K., *J. Med.*, **1989**, *321*, 1022.

[3] Hulme, E.C., et al., *Annu. Rev. Pharmacol.Toxicol.* **1990**, 30, 633.

[4] Eglen, R. M. and Hegde, S. S., *Drug News Perspect.* **1997**, 10(8), 462-469.

[5] Fisher, A., *Invest. Drugs*, **1997**, 6(10), 1395-1411.

[6] Martel, A. M., et al., Drugs Future, **1997**, 22(2), 135-137.

[7] Graul, A. and Castaner, J., Drugs Future, **1996**, 21(11), 1105-1108.

[8] Graul, A., et al., Drugs Future, **1997**, 22(7), 733-737.

All of the above publications are herein incorporated by reference in their entirety to the same extent as if each individual publication was specifically and individually indicated to be incorporated by reference in its entirety.

State of the Art

A receptor is a biological structure with one or more binding domains that reversibly complexes with one or more ligands, where that complexation has biological consequences. Receptors can exist entirely outside the cell (extracellular receptors), within the cell membrane (but presenting sections of the receptor to the extracellular milieu and cytosol), or entirely within the cell (intracellular receptors). They may also function independently of a cell (e.g., clot formation). Receptors within the cell membrane allow a cell to communicate with the space outside of its boundaries (i.e., signaling) as well as to function in the transport of molecules and ions into and out of the cell.

A ligand is a binding partner for a specific receptor or family of receptors. A ligand may be the endogenous ligand for the receptor or alternatively may be a synthetic ligand for the receptor such as a drug, a drug candidate or a pharmacological tool.

The super family of seven transmembrane proteins (7-TMs), also called G-protein coupled receptors (GPCRs), represents one of the most significant classes of membrane bound receptors that communicate changes that occur outside of the cell's boundaries to its interior, triggering a cellular response when appropriate.

The G-proteins, when activated, affect a wide range of downstream effector systems both positively and negatively (e.g., ion channels, protein kinase cascades, transcription, transmigration of adhesion proteins, and the like).

Muscarinic receptors are members of the G-protein coupled receptors that are composed of a family of five receptor sub-types (M_1, M_2, M_3, M_4 and M_5) and are activated by the neurotransmitter acetylcholine[1]. These receptors are widely distributed on multiple organs and tissues and are critical to the maintenance of central and peripheral cholinergic neurotransmission. The regional distribution of these receptor subtypes in the brain and other organs has been documented [1-4]. For example, the M_1 subtype is located primarily in neuronal tissues such as cerebral cortex and autonomic gangia, the M_2 subtype is present mainly in the heart where it mediates cholinergically induced bradycardia, and the M_3 subtype is located predominantly on smooth muscle and salivary glands.

It has been established that the muscarinic receptors are involved in diseases such as chronic obstructive pulmonary disease[5-6], chronic bronchitis, irritable bowel syndrome[7], urinary incontinence[7-8], asthma, rhinitis, spasmodic colitis, chronic cystitis, and nervous polakiurea. Currently, a number of compounds having muscarinic receptor antagonistic activities are being used to treat these diseases. For example, oxybutynin is being used for the treatment of urinary urge incontinence and dicyclomine for the treatment of irritable bowel syndrome. However, these drugs have limited utility as they produce side effects such as dry mouth, blurred vision, and mydriasis. Therefore, there is a need for muscarinic receptor antagonists that will help in the treatment of the above diseases without the adverse side effects.

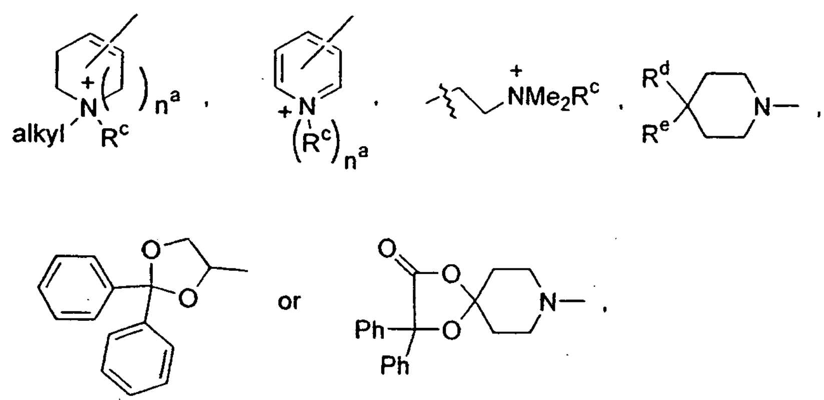
The multibinding compounds of the present invention fulfill this need.

SUMMARY OF THE INVENTION

This invention is directed to novel multibinding compounds (agents) that are muscarinic receptor antagonists and are therefore useful in the treatment and

prevention of diseases such as chronic obstructive pulmonary disease, chronic bronchitis, irritable bowel syndrome, urinary incontinence, and the like.

Accordingly, in one of its composition aspects, this invention provides a multibinding compound comprising of from 2 to 10 ligands covalently attached to one or more linkers, wherein each of said ligands comprises, independently of each other, a muscarinic receptor antagonist or an allosteric modulator of a muscarinic receptor, and pharmaceutically acceptable salts thereof provided that at least one of said ligands is a muscarinic receptor antagonist and further provided that when the multibinding compound comprises 2 or 3 ligands, then only one of the ligands is 11-acetyl-5,11-dihydro-6H-pyrido[2,3b][1,4]benzodiazepin-6-one, N-methylquiniclidine, or a compound of formula:



wherein:

n^a is 0 or 1;

R^c is hydrogen or alkyl;

R^d is hydrogen; and

R^e is $-CO_2CR^f(phenyl)_2$ wherein R^f is hydrogen or hydroxy.

In a second aspect, this invention provides a multibinding compound of Formula (I):

$$(L)_p(X)_q$$
(I)

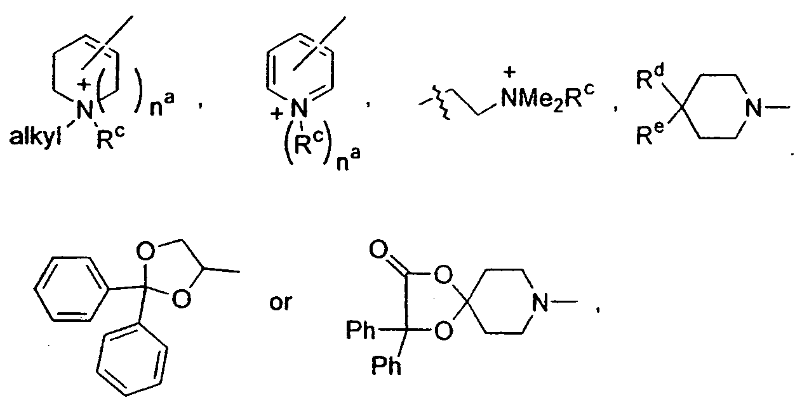
wherein:

each L is, independently of each other, a muscarinic receptor antagonist or an allosteric modulator of a muscarinic receptor;

each X is independently a linker;

p is an integer of from 2 to 10; and

q is an integer of from 1 to 20, and pharmaceutically acceptable salts thereof, provided that at least one of said ligands is a muscarinic receptor antagonist, and further provided that when the multibinding compound comprises of 2 or 3 ligands, then only one of the ligands is 11-acetyl-5,11-dihydro-6H-pyrido[2,3][1,4]benzodiazepin-6-one, N-methylquiniclidine, or a compound of formula:



wherein:

n^a is 0 or 1;

R^c is hydrogen or alkyl;

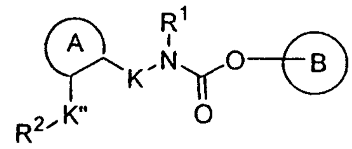
R^d is hydrogen; and

R^e is $-CO_2CR^f(phenyl)_2$ wherein R^f is hydrogen or hydroxy.

Preferably, *q* is less than *p* in the multibinding compounds of this invention.

Preferably, each ligand, L, that is a muscarinic receptor antagonist in the multibinding compound of Formula (I) is independently selected from the group consisting of:

(1) a compound of formula (a):



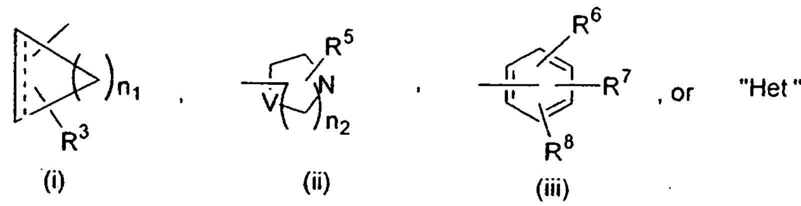
(a)

wherein:

A is an aryl or a heteroaryl ring;

R^1 is hydrogen or alkyl;

R^2 is selected from a group consisting of formula (i), (ii), (iii), or "Het":



wherein:

----- is an optional double bond;

n_1 is an integer of from 1 to 4;

n_2 is an integer of from 1 to 3;

V is -CH-, -O-, -S(O)n_3- (where n_3 is an integer of from 0 to 2), or -NR^4- (wherein R^4 is hydrogen, alkyl, substituted alkyl, aryl, or heteroaryl);

"Het" is a heteroaryl ring which optionally attaches the ligand to a linker;

R^3 is hydrogen, alkyl, amino, substituted amino, -OR^a (where R^a is hydrogen, alkyl, or acyl), or a covalent bond attaching the ligand to a linker;

R^5 is hydrogen, alkyl, amino, substituted amino, -OR^b (where R^b is hydrogen or alkyl), aryl, aralkyl, heteroaralkyl, or a covalent bond attaching the ligand to a linker;

R^6, R^7, and R^8 are, independently of each other, hydrogen, halo, hydroxy, alkoxy, haloalkoxy, carboxy, alkoxycarbonyl, alkyl optionally substituted with one, two or three substituents selected from halo, hydroxy, carboxy, alkoxycarbonyl,

alkylthio, alkylsulfonyl, amino, or substituted amino, or a covalent bond attaching the ligand to a linker;

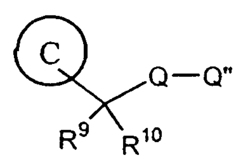
K is a bond or an alkylene group;

K" is a bond, -C(O)-, -$S(O)_{n4}$- (where n_4 is an integer of from 0 to 2), or an alkylene group optionally substituted with a hydroxyl group; and

B is a heterocycloamino group which optionally attaches the ligand to a linker;

provided that at least one of the R^5, R^6, R^7, R^8, "Het", or the heterocycloamino group attaches the ligand to a linker;

(2) a compound of formula (b):



(b)

wherein:

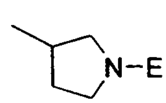
C is an aryl or heteroaryl ring which optionally attaches the ligand to a linker;

R^9 is hydrogen, hydroxy, cyano, aminocarbonyl, alkyl optionally substituted with one, two or three substituents selected from halo, hydroxy, carboxy, alkoxycarbonyl, alkylthio, alkylsulfonyl, amino, substituted amino, or a covalent bond attaching the ligand to a linker;

R^{10} is hydrogen, aryl, heteroaryl, alkyl optionally substituted with one, two or three substituents selected from halo, hydroxy, carboxy, alkoxycarbonyl, alkylthio, alkylsulfonyl, amino, substituted amino, or a covalent bond attaching the ligand to a linker;

Q is a single bond or -C(O)O- such that:

when Q is a bond then, Q" is a group of formula (iv):

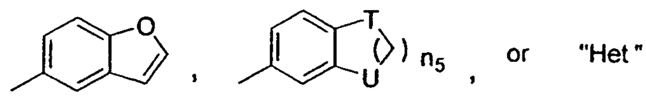


(iv)

where:

E is hydrogen, a covalent bond attaching the ligand to a linker, or $-CH_2$-W-R^{11} wherein W is a single bond or alkylene wherein one of the carbon atoms may optionally be replaced by -O-, -S-, or -NR^8- (wherein R^8 is hydrogen or alkyl); and

R^{11} is a group of formula (v), (vi), or "Het":



(v) (vi)

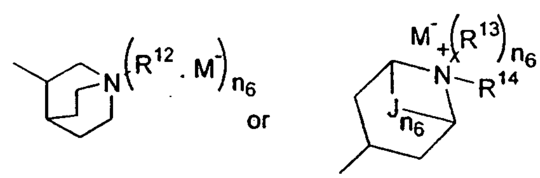
wherein:

T and U are, independently of each other, -O- or $-CH_2$-;

n_5 is an integer of from 1 to 3; and

"Het" is heteroaryl provided that at least one of C, E, R^9, and R^{10} attaches the ligand to a linker; and

when Q is -C(O)O- or -NHC(O)O- then, Q" is a group of formula (vii) or (viii):



(vii) (viii)

wherein:

n_6 is 0 or 1;

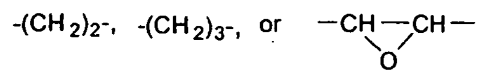
M^- is a counterion;

R^{12} is a covalent bond attaching the ligand to a linker;

R^{13} is alkyl, alkenyl, cycloalkyl, or a covalent bond attaching the ligand to a linker;

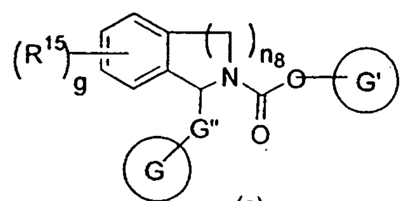
R^{14} is hydrogen, alkyl, or a covalent bond attaching the ligand to a linker; and

J is:



provided that at least one of the C, R^9, R^{10}, R^{12}, R^{13}, and R^{14} attaches the ligand to a linker;

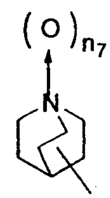
(3) a compound of formula (c):



(c)

wherein:

G' is pyrrolidine, piperidine, or



which optionally attach the ligand to a linker;

n_7 is an 0 or 1, provided that when the nitrogen atom of the quinclidine ring attaches the ligand to the linker then n_7 is 0;

n_8 is 1 or 2;

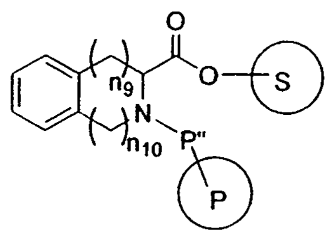
g is an integer of from 0 to 3;

each R^{15} is, independently of each other, hydrogen, halogen, nitro, cyano, hydroxy, alkoxy, carboxy, alkoxycarbonyl, acyl, thio, alkylthio, alkylsulfonyl, alkylsulfinyl, sulfonamido, alkylsulfonamido, carbamoyl, thiocarbamoyl, mono or dialkylcarbamoyl, amino, mono- or dialkylamino, methylenedioxy, ethylenedioxy, alkyl optionally substituted with one, two or three substituents selected from halo, hydroxy, carboxy, alkoxycarbonyl, alkylthio, alkylsulfonyl, amino, or substituted amino, or a covalent bond attaching the ligand to a linker;

G is aryl, heteroaryl, heterocyclyl, or cycloalkyl which optionally attach the ligand to a linker; and

G" is a single bond or an alkylene group provided that at least one of the R^{15}, G, and G" attaches the ligand to a linker;

(4) a compound of formula (d):



(d)

wherein:

n_9 is 1 or 2;

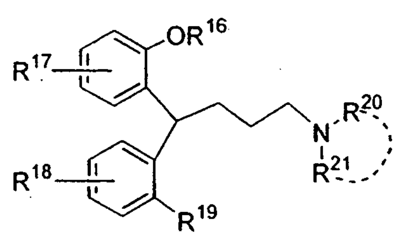
n_{10} is 0 or 1 provided that n_9+n_{10} are 1 or 2;

P is an aryl or heteroaryl ring which optionally attaches the ligand to a linker;

P" is a single bond or an alkylene group;

S is a heterocycloamino ring which optionally attaches the ligand to a linker provided that at least one of the P and S attaches the ligand to a linker;

(5) a compound of formula (e):



(e)

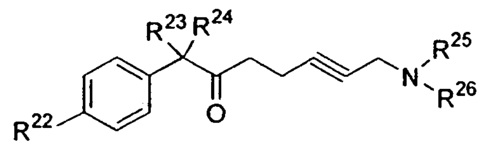
wherein:

R^{16} is hydrogen, alkyl, or a covalent bond attaching the ligand to a linker;

R^{17}, R^{18}, and R^{19} are, independently of each other, hydrogen, alkyl, alkoxy, hydroxy, carbamoyl, sulfanoyl, halo, or a covalent bond attaching the ligand to a linker;

R^{20} and R^{21} are, independently of each other, hydrogen, alkyl or a covalent bond attaching the ligand to a linker; or R^{20} and R^{21} together with the nitrogen atom to which they are attached form a heterocycloamino ring which optionally attaches the ligand to a linker provided that at least one of the R^{16}, R^{17}, R^{18}, R^{19}, R^{20}, and R^{21} attaches the ligand to a linker; or

(6) a compound of formula (f):



(f)

wherein:

R^{22} is hydrogen or halo;

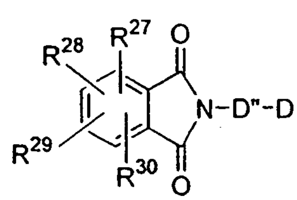
R^{23} is alkyl, cycloalkyl, aryl, heteroaryl, heterocyclyl, or heterocyclylalkyl;

R^{24} is hydroxy, halo, or a covalent bond attaching the ligand to a linker;

R^{25} and R^{26} are, independently of each other, hydrogen, alkyl, aralkyl, or a covalent bond attaching the ligand to a linker, or R^{25} and R^{26} together with the nitrogen atom to which they are attached form a heterocycloamino group which optionally attaches the ligand to a linker provided that at least one of the R^{24}, R^{25}, and R^{26} attaches the ligand to a linker; and

each ligand, L, that is an allosteric modulator of a muscarinic receptor in the multibinding compound of Formula (I) is independently selected from a group consisting of:

(7) a compound of formula (g):



(g)

wherein:

D" is alkylene;

D is $-NR^{31}R^{32}$, $-N^{+}(R^{33}R^{34}R^{35})$ or $-OR^{32}$ where R^{31}, R^{33}, and R^{34} are, independently of each other, hydrogen, alkyl, or aralkyl; and R^{32} and R^{35} represent a covalent bond attaching the ligand to a linker;

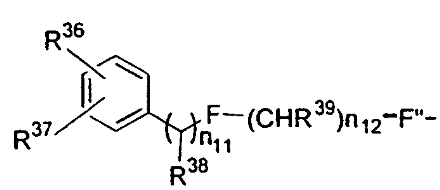
R^{27} is hydrogen, halo, nitro, cyano, hydroxy, alkoxy, carboxy, alkoxycarbonyl, acyl, thio, alkylthio, alkylsulfonyl, alkylsulfinyl, sulfonamido, alkylsulfonamido, carbamoyl, thiocarbamoyl, mono or dialkylcarbamoyl, amino, mono- or dialkylamino, aryl, aryloxy, arylthio, heteroaryl, heteraryloxy, heteroarylthio, heterocyclyl, heterocyclyloxy, aralkyl, heteroaralkyl, or alkyl optionally substituted with one, two or three substituents selected from halo, hydroxy, carboxy, alkoxycarbonyl, alkylthio, alkylsulfonyl, amino, or substituted amino;

R^{28} is hydrogen, halo, nitro, cyano, hydroxy, alkoxy, carboxy, alkoxycarbonyl, acyl, thio, alkylthio, alkylsulfonyl, alkylsulfinyl, sulfonamido, alkylsulfonamido, carbamoyl, thiocarbamoyl, mono or dialkylcarbamoyl, amino, mono- or dialkylamino, or alkyl optionally substituted with one, two, or three substituents selected from halo, hydroxy, carboxy, alkoxycarbonyl, alkylthio, alkylsulfonyl, amino, or substituted amino;

R^{29} and R^{30} are, independently of each other, hydrogen, alkyl, haloalkyl, halo, nitro, cyano, hydroxy, alkoxy, alkoxycarbonyl, acyl, thio, alkylthio, amino, mono- or dialkylamino; or

one of R^{27}, R^{28}, R^{29}, or R^{30} together with the adjacent group forms a methylenedioxy or ethylenedioxy group; or

(8) a compound of formula (h):



(h)

wherein:

n_{11} is an integer of from 1 to 7;

n_{12} is 0 to 7;

F is $-NR^{40}-$, -O-, -S-, or $-CHR^{41}-$ (wherein R^{40} and R^{41} are, independently of each other, hydrogen or alkyl);

F" is a covalent bond, $-OR^{43}$, $-NR^{42}R^{43}$, or $-N^{+}R^{43}R^{44}R^{45}$ wherein R^{42} is hydrogen or alkyl, R^{44} and R^{45} are alkyl, and R^{43} is a covalent bond attaching the ligand to a linker;

R^{36} is hydrogen, halo, nitro, cyano, hydroxy, alkoxy, carboxy, alkoxycarbonyl, acyl, thio, alkylthio, alkylsulfonyl, alkylsulfinyl, sulfonamido, alkylsulfonamido, carbamoyl, thiocarbamoyl, mono or dialkylcarbamoyl, amino, mono- or dialkylamino, aryl, aryloxy, arylthio, heteroaryl, heteraryloxy, heteroarylthio, heterocyclyl, heterocyclyloxy, aralkyl, heteroaralkyl, or alkyl optionally substituted with one, two or three substituents selected from halo, hydroxy, carboxy, alkoxycarbonyl, alkylthio, alkylsulfonyl, amino, or substituted amino;

R^{37} is hydrogen, halo, nitro, cyano, hydroxy, alkoxy, alkoxycarbonyl, acyl, thio, alkylthio, amino, mono- or dialkylamino, aryl, aryloxy, arylthio, heteroaryl, heteraryloxy, heteroarylthio, heterocyclyl, heterocyclyloxy, aralkyl, heteroaralkyl, or alkyl optionally substituted with one, two or three substituents selected from halo, hydroxy, carboxy, alkoxycarbonyl, alkylthio, alkylsulfonyl, amino, or substituted amino; and

R^{38} is hydrogen, alkyl, halo, hydroxy, alkoxy, or a covalent bond attaching the ligand to a linker provided that at least one of R^{38} and R^{43} attaches the ligand to a linker; and

pharmaceutically acceptable salts, individual isomers, mixture of isomers, and prodrugs thereof provided that at least one of the ligands is a muscarinic receptor antagonist.

Preferably, each ligand, L, that is a muscarinic receptor antagonist in the multibinding compound of Formula (I) is independently selected from a group consisting of Darifenacin, Tolterodine, Oxybutynin, YM-46303, YM-58790, 5-(2-isopropylimidazol-1-yl)-3,3-diphenyl-2(3H)furanone which is linked to a linker at the 4-position of imidazole ring, 3,3-diphenyl-2(3H)furanone which is linked to a linker at the 5-position of the furanone ring (disclosed in *J. Med. Chem.*, 35, 4415-4424, 1992), 3-[4-(2-chlorobenzyl)piperizin-1-yl)-1-cyclobutyl-1-phenyl-2-propanone which is linked to a linker via the phenyl ring of the benzyl moiety, 3-(piperizin-1-yl)-1-cyclobutyl-1-phenyl-2-propanone which is linked to a linker via the piperizine ring, 3-[4-(benzylpiperizin-1-yl)-1-cyclobutyl-1-phenyl-2-propanone which is linked to a linker via the phenyl ring of the benzyl moiety, 3-[4-benzylpiperizin-1-yl)-1,1-diphenyl-2-propanone which is linked to a linker via the phenyl ring of the benzyl moiety, 3-(piperizin-1-yl)-1,1-diphenyl-2-propanone which is linked to a linker via the piperizine ring (disclosed in *J. Med. Chem.*, 36, 610-616, 1993), the derivatives thereof.

Preferably, each linker, X, in the multibinding compound of Formula (I) independently has the formula:

$$-X^a-Z-(Y^a-Z)_m-Y^b-Z-X^a-$$

wherein

m is an integer of from 0 to 20;

X^a at each separate occurrence is selected from the group consisting of -O-, -S-, -NR-, -C(O)-, -C(O)O-, -C(O)NR-, -C(S), -C(S)O-, -C(S)NR- or a covalent bond where R is as defined below;

Z at each separate occurrence is selected from the group consisting of alkylene, substituted alkylene, cycloalkylene, substituted cylcoalkylene, alkenylene, substituted alkenylene, alkynylene, substituted alkynylene, cycloalkenylene, substituted cycloalkenylene, arylene, heteroarylene, heterocyclene, or a covalent bond;

Y^a and Y^b at each separate occurrence are selected from the group consisting of -O-, -C(O)-, -OC(O)-, -C(O)O-, -NR-, -S(O)n-, -C(O)NR'-, -NR' C(O)-, -NR' C(O)NR'-, -NR' C(S)NR'-, -C(=NR')-NR'-, -NR'-C(=NR')-, -OC(O)-NR'-, -NR'-C(O)-O-, -N=C(X^a)-NR'-, -NR'-C(X^a)=N-,-P(O)(OR')-O-, -O-P(O)(OR')-, -S(O)$_n$CR' R"-, -S(O)$_n$-NR'-, -NR'-S(O)$_n$-, -S-S-, and a covalent bond; where *n* is 0, 1 or 2; and R, R' and R" at each separate occurrence are selected from the group consisting of hydrogen, alkyl, substituted alkyl, cycloalkyl, substituted cycloalkyl, alkenyl, substituted alkenyl, cycloalkenyl, substituted cycloalkenyl, alkynyl, substituted alkynyl, aryl, heteroaryl and heterocyclic.

In a third aspect, this invention provides a pharmaceutical composition comprising a pharmaceutically acceptable carrier and an effective amount of a multibinding compound comprising from 2 to 10 ligands covalently attached to one or more linkers, wherein each of said ligands wherein each of said ligands comprises, independently of each other, a muscarinic receptor antagonist or an allosteric modulator of a muscarinic receptor provided that at least one of said ligands is a muscarinic receptor antagonist, and pharmaceutically acceptable salts thereof.

In a fourth aspect, this invention provides a method of treating diseases mediated by a muscarinic receptor in a mammal, said method comprising administering to said mammal a therapeutically effective amount of a pharmaceutical composition comprising a pharmaceutically acceptable carrier and a multibinding compound comprising from 2 to 10 ligands covalently attached to one or more linkers, wherein each of said ligands, comprises, independently of each other, a muscarinic receptor antagonist or an allosteric modulator of a muscarinic receptor provided that at least one of said ligands is a muscarinic receptor antagonist, and pharmaceutically acceptable salts thereof.

In a fifth aspect, this invention provides methods for preparing a multibinding compound of Formula (I).

In a sixth aspect, this invention is directed to general synthetic methods for generating large libraries of diverse multimeric compounds which multimeric compounds are candidates for possessing multibinding properties for a muscarinic receptor. The diverse multimeric compound libraries provided by this invention are synthesized by combining a linker or linkers with a ligand or ligands to provide for a library of multimeric compounds wherein the linker and ligand each have complementary functional groups permitting covalent linkage. The library of linkers is preferably selected to have diverse properties such as valency, linker length, linker geometry and rigidity, hydrophilicity or hydrophobicity, amphiphilicity, acidity, basicity and polarization. The library of ligands is preferably selected to have diverse attachment points on the same ligand, different functional groups at the same site of otherwise the same ligand, and the like.

This invention is also directed to libraries of diverse multimeric compounds which multimeric compounds are candidates for possessing multibinding properties for a muscarinic receptor. These libraries are prepared via the methods described above and permit the rapid and efficient evaluation of what molecular constraints impart multibinding properties to a ligand or a class of ligands targeting a muscarinic receptor.

Accordingly, in one of its method aspects, this invention is directed to a method for identifying multimeric ligand compounds possessing multibinding properties for a muscarinic receptor which method comprises:

(a) identifying a ligand or a mixture of ligands wherein each ligand contains at least one reactive functionality;

(b) identifying a library of linkers wherein each linker in said library comprises at least two functional groups having complementary reactivity to at least one of the reactive functional groups of the ligand;

(c) preparing a multimeric ligand compound library by combining at least two stoichiometric equivalents of the ligand or mixture of ligands identified in (a) with the library of linkers identified in (b) under conditions wherein the

complementary functional groups react to form a covalent linkage between said linker and at least two of said ligands; and

(d) assaying the multimeric ligand compounds produced in (c) above to identify multimeric ligand compounds possessing multibinding properties for a muscarinic receptor.

In another of its method aspects, this invention is directed to a method for identifying multimeric ligand compounds possessing multibinding properties for a muscarinic receptor which method comprises:

(a) identifying a library of ligands wherein each ligand contains at least one reactive functionality;

(b) identifying a linker or mixture of linkers wherein each linker comprises at least two functional groups having complementary reactivity to at least one of the reactive functional groups of the ligand;

(c) preparing a multimeric ligand compound library by combining at least two stoichiometric equivalents of the library of ligands identified in (a) with the linker or mixture of linkers identified in (b) under conditions wherein the complementary functional groups react to form a covalent linkage between said linker and at least two of said ligands; and

(d) assaying the multimeric ligand compounds produced in (c) above to identify multimeric ligand compounds possessing multibinding properties for a muscarinic receptor.

The preparation of the multimeric ligand compound library is achieved by either the sequential or concurrent combination of the two or more stoichiometric equivalents of the ligands identified in (a) with the linkers identified in (b). Sequential addition is preferred when a mixture of different ligands is employed to ensure heterodimeric or multimeric compounds are prepared. Concurrent addition of the ligands occurs when at least a portion of the multimer comounds prepared are homomultimeric compounds.

The assay protocols recited in (d) can be conducted on the multimeric ligand compound library produced in (c) above, or preferably, each member of the library is isolated by preparative liquid chromatography mass spectrometry (LCMS).

In one of its composition aspects, this invention is directed to a library of multimeric ligand compounds which may possess multivalent properties for a muscarinic receptor which library is prepared by the method comprising:

(a) identifying a ligand or a mixture of ligands wherein each ligand contains at least one reactive functionality;

(b) identifying a library of linkers wherein each linker in said library comprises at least two functional groups having complementary reactivity to at least one of the reactive functional groups of the ligand; and

(c) preparing a multimeric ligand compound library by combining at least two stoichiometric equivalents of the ligand or mixture of ligands identified in (a) with the library of linkers identified in (b) under conditions wherein the complementary functional groups react to form a covalent linkage between said linker and at least two of said ligands.

In another of its composition aspects, this invention is directed to a library of multimeric ligand compounds which may possess multivalent properties for a muscarinic receptor which library is prepared by the method comprising:

(a) identifying a library of ligands wherein each ligand contains at least one reactive functionality;

(b) identifying a linker or mixture of linkers wherein each linker comprises at least two functional groups having complementary reactivity to at least one of the reactive functional groups of the ligand; and

(c) preparing a multimeric ligand compound library by combining at least two stoichiometric equivalents of the library of ligands identified in (a) with the linker or mixture of linkers identified in (b) under conditions wherein the complementary functional groups react to form a covalent linkage between said linker and at least two of said ligands.

In a preferred embodiment, the library of linkers employed in either the methods or the library aspects of this invention is selected from the group comprising flexible linkers, rigid linkers, hydrophobic linkers, hydrophilic linkers, linkers of different geometry, acidic linkers, basic linkers, linkers of different polarization and amphiphilic linkers. For example, in one embodiment, each of the linkers in the linker library may comprise linkers of different chain length and/or having different complementary reactive groups. Such linker lengths can preferably range from about 2 to 100Å.

In another preferred embodiment, the ligand or mixture of ligands is selected to have reactive functionality at different sites on said ligands in order to provide for a range of orientations of said ligand on said multimeric ligand compounds. Such reactive functionality includes, by way of example, carboxylic acids, carboxylic acid halides, carboxyl esters, amines, halides, isocyanates, vinyl unsaturation, ketones, aldehydes, thiols, alcohols, anhydrides, and precursors thereof. It is understood, of course, that the reactive functionality on the ligand is selected to be complementary to at least one of the reactive groups on the linker so that a covalent linkage can be formed between the linker and the ligand.

In other embodiments, the multimeric ligand compound is homomeric (i.e., each of the ligands is the same, although it may be attached at different points) or heterodimeric (i.e., at least one of the ligands is different from the other ligands).

In addition to the combinatorial methods described herein, this invention provides for an interative process for rationally evaluating what molecular constraints impart multibinding properties to a class of multimeric compounds or ligands targeting a muscarinic receptor. Specifically, this method aspect is directed to a method for identifying multimeric ligand compounds possessing multibinding properties for a muscarinic receptor which method comprises:

(a) preparing a first collection or iteration of multimeric compounds which is prepared by contacting at least two stoichiometric equivalents of the ligand or mixture of ligands which target a receptor with a linker or mixture of linkers wherein said ligand or mixture of ligands comprises at least one reactive

functionality and said linker or mixture of linkers comprises at least two functional groups having complementary reactivity to at least one of the reactive functional groups of the ligand wherein said contacting is conducted under conditions wherein the complementary functional groups react to form a covalent linkage between said linker and at least two of said ligands;

(b) assaying said first collection or iteration of multimeric compounds to assess which if any of said multimeric compounds possess multibinding properties for a muscarinic receptor;

(c) repeating the process of (a) and (b) above until at least one multimeric compound is found to possess multibinding properties for a muscarinic receptor;

(d) evaluating what molecular constraints imparted multibinding properties to the multimeric compound or compounds found in the first iteration recited in (a)- (c) above;

(e) creating a second collection or iteration of multimeric compounds which elaborates upon the particular molecular constraints imparting multibinding properties to the multimeric compound or compounds found in said first iteration;

(f) evaluating what molecular constraints imparted enhanced multibinding properties to the multimeric compound or compounds found in the second collection or iteration recited in (e) above;

(g) optionally repeating steps (e) and (f) to further elaborate upon said molecular constraints.

Preferably, steps (e) and (f) are repeated at least two times, more preferably at from 2-50 times, even more preferably from 3 to 50 times, and still more preferably at least 5-50 times.

BRIEF DESCRIPTION OF THE DRAWINGS

FIG. 1 illustrates examples of multibinding compounds comprising 2 ligands attached in different formats to a linker.

FIG. 2 illustrates examples of multibinding compounds comprising 3 ligands attached in different formats to a linker.

FIG. 3 illustrates examples of multibinding compounds comprising 4 ligands attached in different formats to a linker.

FIG. 4 illustrates examples of multibinding compounds comprising >4 ligands attached in different formats to a linker.

DETAILED DESCRIPTION OF THE INVENTION

Definitions

This invention is directed to multibinding compounds which are muscarinic receptor antagonists, pharmaceutical compositions containing such compounds and methods for treating diseases mediated by a muscarinic receptor in mammals. When discussing such compounds, compositions or methods, the following terms have the following meanings unless otherwise indicated. Any undefined terms have their art recognized meanings.

The term "alkyl" refers to a monoradical branched or unbranched saturated hydrocarbon chain preferably having from 1 to 40 carbon atoms, more preferably 1 to 10 carbon atoms, and even more preferably 1 to 6 carbon atoms. This term is exemplified by groups such as methyl, ethyl, *n*-propyl, *iso*-propyl, *n*-butyl, *iso*-butyl, *n*-hexyl, *n*-decyl, tetradecyl, and the like.

The term "substituted alkyl" refers to an alkyl group as defined above having from 1 to 5 substituents selected from the group consisting of alkoxy, substituted alkoxy, cycloalkyl, substituted cycloalkyl, cycloalkenyl, substituted cycloalkenyl, acyl, acylamino, acyloxy, amino, aminoacyl, aminoacyloxy, oxyaminoacyl, azido, cyano, halogen, hydroxyl, keto, thioketo, carboxyl, carboxylalkyl, thioaryloxy, thioheteroaryloxy, thioheterocyclooxy, thiol, thioalkoxy, substituted thioalkoxy, aryl, aryloxy, heteroaryl, heteroaryloxy, heterocyclic, heterocyclooxy, hydroxyamino, alkoxyamino, nitro, -SO-alkyl, -SO-aryl, -SO-heteroaryl, -SO_2-alkyl, -SO_2-aryl, -SO_2-heteroaryl, and -NR^aR^b, wherein R^a and R^b may be the same or different and and are chosen from hydrogen,

optionally substituted alkyl, cycloalkyl, alkenyl, cycloalkenyl, alkynyl, aryl, heteroaryl and heterocyclic. The term substituted alkyl also includes an alkyl chain where in one or more of the carbon atoms have been replaced with a heteroatom such as -O-, -S(O)n- (where n is 0 to 2), -NR- (where R is hydrogen or alkyl). This term is exemplified by groups such as hydroxymethyl, hydroxyethyl, hydroxypropyl, 2-aminoethyl, 3-aminopropyl, 2-methylaminoethyl, 3-dimethylaminopropyl, 2-sulfonamidoethyl, 2-carboxyethyl, and the like.

The term "alkylene" refers to a diradical of a branched or unbranched saturated hydrocarbon chain, preferably having from 1 to 40 carbon atoms, more preferably 1 to 10 carbon atoms and even more preferably 1 to 6 carbon atoms. This term is exemplified by groups such as methylene ($-CH_2-$), ethylene ($-CH_2CH_2-$), the propylene isomers (e.g., $-CH_2CH_2CH_2-$ and $-CH(CH_3)CH_2-$) and the like.

The term "substituted alkylene" refers to an alkylene group, as defined above, having from 1 to 5 substituents, and preferably 1 to 3 substituents, selected from the group consisting of alkoxy, substituted alkoxy, cycloalkyl, substituted cycloalkyl, cycloalkenyl, substituted cycloalkenyl, acyl, acylamino, acyloxy, amino, substituted amino, aminoacyl, aminoacyloxy, oxyaminoacyl, azido, cyano, halogen, hydroxyl, keto, thioketo, carboxyl, carboxylalkyl, thioaryloxy, thioheteroaryloxy, thioheterocyclooxy, thiol, thioalkoxy, substituted thioalkoxy, aryl, aryloxy, heteroaryl, heteroaryloxy, heterocyclic, heterocyclooxy, hydroxyamino, alkoxyamino, nitro, -SO-alkyl, -SO-substituted alkyl, -SO-aryl, -SO-heteroaryl, $-SO_2$-alkyl, $-SO_2$-substituted alkyl, $-SO_2$-aryl and $-SO_2$-heteroaryl. Additionally, such substituted alkylene groups include those where 2 substituents on the alkylene group are fused to form one or more cycloalkyl, substituted cycloalkyl, cycloalkenyl, substituted cycloalkenyl, aryl, heterocyclic or heteroaryl groups fused to the alkylene group. Preferably such fused groups contain from 1 to 3 fused ring structures.

The term "alkaryl" or "aralkyl" refers to the groups -alkylene-aryl and -substituted alkylene-aryl where alkylene, substituted alkylene and aryl are defined herein. Such alkaryl groups are exemplified by benzyl, phenethyl and the like.

The term "alkoxy" refers to the groups alkyl-O-, alkenyl-O-, cycloalkyl-O-, cycloalkenyl-O-, and alkynyl-O-, where alkyl, alkenyl, cycloalkyl, cycloalkenyl, and alkynyl are as defined herein. Preferred alkoxy groups are alkyl-O- and include, by way of example, methoxy, ethoxy, *n*-propoxy, *iso*-propoxy, *n*-butoxy, *tert*-butoxy, *sec*-butoxy, *n*-pentoxy, *n*-hexoxy, 1,2-dimethylbutoxy, and the like.

The term "substituted alkoxy" refers to the groups substituted alkyl-O-, substituted alkenyl-O-, substituted cycloalkyl-O-, substituted cycloalkenyl-O-, and substituted alkynyl-O- where substituted alkyl, substituted alkenyl, substituted cycloalkyl, substituted cycloalkenyl and substituted alkynyl are as defined herein.

The term "haloalkoxy" refers to the groups alkyl-O- wherein one or more hydrogen atoms on the alkyl group have been substituted with a halo group and include, by way of examples, groups such as trifluoromethoxy, and the like.

The term "alkylalkoxy" refers to the groups -alkylene-O-alkyl, alkylene-O-substituted alkyl, substituted alkylene-O-alkyl, and substituted alkylene-O-substituted alkyl wherein alkyl, substituted alkyl, alkylene and substituted alkylene are as defined herein. Preferred alkylalkoxy groups are alkylene-O-alkyl and include, by way of example, methylenemethoxy ($-CH_2OCH_3$), ethylenemethoxy ($-CH_2CH_2OCH_3$), *n*-propylene-*iso*-propoxy ($-CH_2CH_2CH_2OCH(CH_3)_2$), methylene-*t*-butoxy ($-CH_2-O-C(CH_3)_3$), and the like.

The term "alkylthioalkoxy" refers to the group -alkylene-S-alkyl, alkylene-S-substituted alkyl, substituted alkylene-S-alkyl and substituted alkylene-S-substituted alkyl wherein alkyl, substituted alkyl, alkylene and substituted alkylene are as defined herein. Preferred alkylthioalkoxy groups are alkylene-S-alkyl and include, by way of example, methylenethiomethoxy ($-CH_2SCH_3$), ethylenethiomethoxy ($-CH_2CH_2SCH_3$), *n*-propylene-*iso*-thiopropoxy ($-CH_2CH_2CH_2SCH(CH_3)_2$), methylene-*t*-thiobutoxy ($-CH_2SC(CH_3)_3$), and the like.

The term "alkenyl" refers to a monoradical of a branched or unbranched unsaturated hydrocarbon group preferably having from 2 to 40 carbon atoms, more preferably 2 to 10 carbon atoms and even more preferably 2 to 6 carbon atoms and having at least 1 and preferably from 1-6 sites of vinyl unsaturation. Preferred

alkenyl groups include ethenyl ($-CH=CH_2$), *n*-propenyl ($-CH_2CH=CH_2$), *iso*-propenyl ($-C(CH_3)=CH_2$), and the like.

The term "substituted alkenyl" refers to an alkenyl group as defined above having from 1 to 5 substituents, and preferably 1 to 3 substituents, selected from the group consisting of alkoxy, substituted alkoxy, cycloalkyl, substituted cycloalkyl, cycloalkenyl, substituted cycloalkenyl, acyl, acylamino, acyloxy, amino, substituted amino, aminoacyl, aminoacyloxy, oxyaminoacyl, azido, cyano, halogen, hydroxyl, keto, thioketo, carboxyl, carboxylalkyl, thioaryloxy, thioheteroaryloxy, thioheterocyclooxy, thiol, thioalkoxy, substituted thioalkoxy, aryl, aryloxy, heteroaryl, heteroaryloxy, heterocyclic, heterocyclooxy, hydroxyamino, alkoxyamino, nitro, -SO-alkyl, -SO-substituted alkyl, -SO-aryl, -SO-heteroaryl, $-SO_2$-alkyl, $-SO_2$-substituted alkyl, $-SO_2$-aryl and $-SO_2$-heteroaryl.

The term "alkenylene" refers to a diradical of a branched or unbranched unsaturated hydrocarbon group preferably having from 2 to 40 carbon atoms, more preferably 2 to 10 carbon atoms and even more preferably 2 to 6 carbon atoms and having at least 1 and preferably from 1-6 sites of vinyl unsaturation. This term is exemplified by groups such as ethenylene ($-CH=CH-$), the propenylene isomers (e.g., $-CH_2CH=CH-$ or $-C(CH_3)=CH-$), and the like.

The term "substituted alkenylene" refers to an alkenylene group as defined above having from 1 to 5 substituents, and preferably from 1 to 3 substituents, selected from the group consisting of alkoxy, substituted alkoxy, cycloalkyl, substituted cycloalkyl, cycloalkenyl, substituted cycloalkenyl, acyl, acylamino, acyloxy, amino, substituted amino, aminoacyl, aminoacyloxy, oxyaminoacyl, azido, cyano, halogen, hydroxyl, keto, thioketo, carboxyl, carboxylalkyl, thioaryloxy, thioheteroaryloxy, thioheterocyclooxy, thiol, thioalkoxy, substituted thioalkoxy, aryl, aryloxy, heteroaryl, heteroaryloxy, heterocyclic, heterocyclooxy, hydroxyamino, alkoxyamino, nitro, -SO-alkyl, -SO-substituted alkyl, -SO-aryl, -SO-heteroaryl, $-SO_2$-alkyl, $-SO_2$-substituted alkyl, $-SO_2$-aryl and $-SO_2$-heteroaryl. Additionally, such substituted alkenylene groups include those where 2 substituents on the alkenylene group are fused to form one or more cycloalkyl, substituted

cycloalkyl, cycloalkenyl, substituted cycloalkenyl, aryl, heterocyclic or heteroaryl groups fused to the alkenylene group.

The term "alkynyl" refers to a monoradical of an unsaturated hydrocarbon preferably having from 2 to 40 carbon atoms, more preferably 2 to 20 carbon atoms and even more preferably 2 to 6 carbon atoms and having at least 1 and preferably from 1-6 sites of acetylene (triple bond) unsaturation. Preferred alkynyl groups include ethynyl (-C≡CH), propargyl ($-CH_2C≡CH$), and the like.

The term "substituted alkynyl" refers to an alkynyl group as defined above having from 1 to 5 substituents, and preferably 1 to 3 substituents, selected from the group consisting of alkoxy, substituted alkoxy, cycloalkyl, substituted cycloalkyl, cycloalkenyl, substituted cycloalkenyl, acyl, acylamino, acyloxy, amino, substituted amino, aminoacyl, aminoacyloxy, oxyaminoacyl, azido, cyano, halogen, hydroxyl, keto, thioketo, carboxyl, carboxylalkyl, thioaryloxy, thioheteroaryloxy, thioheterocyclooxy, thiol, thioalkoxy, substituted thioalkoxy, aryl, aryloxy, heteroaryl, heteroaryloxy, heterocyclic, heterocyclooxy, hydroxyamino, alkoxyamino, nitro, -SO-alkyl, -SO-substituted alkyl, -SO-aryl, -SO-heteroaryl, $-SO_2$-alkyl, $-SO_2$-substituted alkyl, $-SO_2$-aryl, and $-SO_2$-heteroaryl.

The term "alkynylene" refers to a diradical of an unsaturated hydrocarbon preferably having from 2 to 40 carbon atoms, more preferably 2 to 10 carbon atoms and even more preferably 2 to 6 carbon atoms and having at least 1 and preferably from 1-6 sites of acetylene (triple bond) unsaturation. Preferred alkynylene groups include ethynylene (-C≡C-), propargylene ($-CH_2C≡C-$), and the like.

The term "substituted alkynylene" refers to an alkynylene group as defined above having from 1 to 5 substituents, and preferably 1 to 3 substituents, selected from the group consisting of alkoxy, substituted alkoxy, cycloalkyl, substituted cycloalkyl, cycloalkenyl, substituted cycloalkenyl, acyl, acylamino, acyloxy, amino, substituted amino, aminoacyl, aminoacyloxy, oxyaminoacyl, azido, cyano, halogen, hydroxyl, keto, thioketo, carboxyl, carboxylalkyl, thioaryloxy, thioheteroaryloxy, thioheterocyclooxy, thiol, thioalkoxy, substituted thioalkoxy, aryl, aryloxy,

heteroaryl, heteroaryloxy, heterocyclic, heterocyclooxy, hydroxyamino, alkoxyamino, nitro, -SO-alkyl, -SO-substituted alkyl, -SO-aryl, -SO-heteroaryl, -SO_2-alkyl, -SO_2-substituted alkyl, -SO_2-aryl and -SO_2-heteroaryl.

The term "acyl" refers to the groups HC(O)-, alkyl-C(O)-, substituted alkyl-C(O)-, cycloalkyl-C(O)-, substituted cycloalkyl-C(O)-, cycloalkenyl-C(O)-, substituted cycloalkenyl-C(O)-, aryl-C(O)-, heteroaryl-C(O)- and heterocyclic-C(O)- where alkyl, substituted alkyl, cycloalkyl, substituted cycloalkyl, cycloalkenyl, substituted cycloalkenyl, aryl, heteroaryl, and heterocyclic are as defined herein.

The term "acylamino" or "aminocarbonyl" refers to the group -C(O)NRR where each R is independently hydrogen, alkyl, substituted alkyl, aryl, heteroaryl, heterocyclic or where both R groups are joined to form a heterocyclic group (e.g., morpholino) wherein alkyl, substituted alkyl, aryl, heteroaryl, and heterocyclic are as defined herein.

The term "aminoacyl" refers to the group -NRC(O)R where each R is independently hydrogen, alkyl, substituted alkyl, aryl, heteroaryl, or heterocyclic wherein alkyl, substituted alkyl, aryl, heteroaryl, and heterocyclic are as defined herein.

The term "aminoacyloxy" or "alkoxycarbonylamino" refers to the group -NRC(O)OR where each R is independently hydrogen, alkyl, substituted alkyl, aryl, heteroaryl, or heterocyclic wherein alkyl, substituted alkyl, aryl, heteroaryl, and heterocyclic are as defined herein.

The term "acyloxy" refers to the groups alkyl-C(O)O-, substituted alkyl-C(O)O-, cycloalkyl-C(O)O-, substituted cycloalkyl-C(O)O-, aryl-C(O)O-, heteroaryl-C(O)O-, and heterocyclic-C(O)O- wherein alkyl, substituted alkyl, cycloalkyl, substituted cycloalkyl, aryl, heteroaryl, and heterocyclic are as defined herein.

The term "aryl" refers to an unsaturated aromatic carbocyclic group of from 6 to 20 carbon atoms having a single ring (e.g., phenyl) or multiple condensed (fused) rings (e.g., naphthyl or anthryl). Preferred aryls include phenyl, naphthyl

and the like. Unless otherwise constrained by the definition for the aryl substituent, such aryl groups can optionally be substituted with from 1 to 5 substituents, preferably 1 to 3 substituents, selected from the group consisting of acyloxy, hydroxy, thiol, acyl, alkyl, alkoxy, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, substituted alkyl, substituted alkoxy, substituted alkenyl, substituted alkynyl, substituted cycloalkyl, substituted cycloalkenyl, amino, substituted amino, aminoacyl, acylamino, alkaryl, aryl, aryloxy, azido, carboxyl, carboxylalkyl, cyano, halo, nitro, heteroaryl, heteroaryloxy, heterocyclic, heterocyclooxy, aminoacyloxy, oxyacylamino, thioalkoxy, substituted thioalkoxy, thioaryloxy, thioheteroaryloxy, -SO-alkyl, -SO-substituted alkyl, -SO-aryl, -SO-heteroaryl, -SO_2-alkyl, -SO_2-substituted alkyl, -SO_2-aryl, -SO_2-heteroaryl and trihalomethyl. Preferred aryl substituents include alkyl, alkoxy, halo, cyano, nitro, trihalomethyl, and thioalkoxy.

The term "aryloxy" refers to the group aryl-O- wherein the aryl group is as defined above including optionally substituted aryl groups as also defined above.

The term " arylene " refers to the diradical derived from aryl (including substituted aryl) as defined above and is exemplified by 1,2-phenylene, 1,3-phenylene, 1,4-phenylene, 1,2-naphthylene and the like.

The term " amino " refers to the group -NH_2.

The term " substituted amino " refers to the group -NRR where each R is independently selected from the group consisting of hydrogen, alkyl, substituted alkyl, cycloalkyl, substituted cycloalkyl, alkenyl, substituted alkenyl, cycloalkenyl, substituted cycloalkenyl, alkynyl, substituted alkynyl, aryl, heteroaryl, and heterocyclic provided that both R's are not hydrogen.

The term " carboxyalkyl" or "alkoxycarbonyl" refers to the groups "-C(O)O-alkyl", "-C(O)O-substituted alkyl", "-C(O)O-cycloalkyl", "-C(O)O-substituted cycloalkyl", "-C(O)O-alkenyl", "-C(O)O-substituted alkenyl", "-C(O)O-alkynyl" and "-C(O)O-substituted alkynyl" where alkyl, substituted alkyl, cycloalkyl, substituted cycloalkyl, alkenyl, substituted alkenyl, alkynyl and substituted alkynyl alkynyl are as defined herein.

The term "cycloalkyl" refers to cyclic alkyl groups of from 3 to 20 carbon atoms having a single cyclic ring or multiple condensed rings. Such cycloalkyl groups include, by way of example, single ring structures such as cyclopropyl, cyclobutyl, cyclopentyl, cyclooctyl, and the like, or multiple ring structures such as adamantanyl, and the like.

The term "substituted cycloalkyl" refers to cycloalkyl groups having from 1 to 5 substituents, and preferably 1 to 3 substituents, selected from the group consisting of alkoxy, substituted alkoxy, cycloalkyl, substituted cycloalkyl, cycloalkenyl, substituted cycloalkenyl, acyl, acylamino, acyloxy, amino, substituted amino, aminoacyl, aminoacyloxy, oxyaminoacyl, azido, cyano, halogen, hydroxyl, keto, thioketo, carboxyl, carboxylalkyl, thioaryloxy, thioheteroaryloxy, thioheterocyclooxy, thiol, thioalkoxy, substituted thioalkoxy, aryl, aryloxy, heteroaryl, heteroaryloxy, heterocyclic, heterocyclooxy, hydroxyamino, alkoxyamino, nitro, -SO-alkyl, -SO-substituted alkyl, -SO-aryl, -SO-heteroaryl, -SO_2-alkyl, -SO_2-substituted alkyl, -SO_2-aryl and -SO_2-heteroaryl.

The term "cycloalkenyl" refers to cyclic alkenyl groups of from 4 to 20 carbon atoms having a single cyclic ring and at least one point of internal unsaturation. Examples of suitable cycloalkenyl groups include, for instance, cyclobut-2-enyl, cyclopent-3-enyl, cyclooct-3-enyl, and the like.

The term "substituted cycloalkenyl" refers to cycloalkenyl groups having from 1 to 5 substituents, and preferably 1 to 3 substituents, selected from the group consisting of alkoxy, substituted alkoxy, cycloalkyl, substituted cycloalkyl, cycloalkenyl, substituted cycloalkenyl, acyl, acylamino, acyloxy, amino, substituted amino, aminoacyl, aminoacyloxy, oxyaminoacyl, azido, cyano, halogen, hydroxyl, keto, thioketo, carboxyl, carboxylalkyl, thioaryloxy, thioheteroaryloxy, thioheterocyclooxy, thiol, thioalkoxy, substituted thioalkoxy, aryl, aryloxy, heteroaryl, heteroaryloxy, heterocyclic, heterocyclooxy, hydroxyamino, alkoxyamino, nitro, -SO-alkyl, -SO-substituted alkyl, -SO-aryl, -SO-heteroaryl, -SO_2-alkyl, -SO_2-substituted alkyl, -SO_2-aryl and -SO_2-heteroaryl.

The term "halo" or "halogen" refers to fluoro, chloro, bromo and iodo.

The term "heteroaryl" refers to an aromatic group of from 1 to 15 carbon atoms and 1 to 4 heteroatoms selected from oxygen, nitrogen and sulfur within at least one ring (if there is more than one ring). Unless otherwise constrained by the definition for the heteroaryl substituent, such heteroaryl groups can be optionally substituted with 1 to 5 substituents, preferably 1 to 3 substituents, selected from the group consisting of acyloxy, hydroxy, thiol, acyl, alkyl, alkoxy, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, substituted alkyl, substituted alkoxy, substituted alkenyl, substituted alkynyl, substituted cycloalkyl, substituted cycloalkenyl, amino, substituted amino, aminoacyl, acylamino, alkaryl, aryl, aryloxy, azido, carboxyl, carboxylalkyl, cyano, halo, nitro, heteroaryl, heteroaryloxy, heterocyclic, heterocyclooxy, aminoacyloxy, oxyacylamino, thioalkoxy, substituted thioalkoxy, thioaryloxy, thioheteroaryloxy, -SO-alkyl, -SO-substituted alkyl, -SO-aryl, -SO-heteroaryl, -SO_2-alkyl, -SO_2-substituted alkyl, -SO_2-aryl, -SO_2-heteroaryl and trihalomethyl. Preferred aryl substituents include alkyl, alkoxy, halo, cyano, nitro, trihalomethyl, and thioalkoxy. Such heteroaryl groups can have a single ring (e.g., pyridyl or furyl) or multiple condensed rings (e.g., indolizinyl or benzothienyl). Preferred heteroaryls include pyridyl, pyrrolyl and furyl.

The term "heteroaralkyl" refers to the groups -alkylene-heteroaryl where alkylene and heteroaryl are defined herein. Such heteroaralkyl groups are exemplified by pyridylmethyl, pyridylethyl, indolylmethyl, and the like.

The term "heteroaryloxy" refers to the group heteroaryl-O-.

The term " heteroarylene " refers to the diradical group derived from heteroaryl (including substltuted heteroaryl), as defined above, and is exemplified by the groups 2,6-pyridylene, 2,4-pyridiylene, 1,2-quinolinylene, 1,8-quinolinylene, 1,4-benzofuranylene, 2,5-pyridnylene, 2,5-indolenyl, and the like.

The term "heterocycle" or "heterocyclic" or refers to a monoradical saturated unsaturated group having a single ring or multiple condensed rings, from 1 to 40 carbon atoms and from 1 to 10 hetero atoms, preferably 1 to 4 heteroatoms, selected from nitrogen, sulfur, phosphorus, and/or oxygen within the ring. Unless otherwise constrained by the definition for the heterocyclic substituent, such heterocyclic

groups can be optionally substituted with 1 to 5, and preferably 1 to 3 substituents, selected from the group consisting of alkoxy, substituted alkoxy, cycloalkyl, substituted cycloalkyl, cycloalkenyl, substituted cycloalkenyl, acyl, acylamino, acyloxy, amino, substituted amino, aminoacyl, aminoacyloxy, oxyaminoacyl, azido, cyano, halogen, hydroxyl, keto, thioketo, carboxyl, carboxylalkyl, thioaryloxy, thioheteroaryloxy, thioheterocyclooxy, thiol, thioalkoxy, substituted thioalkoxy, aryl, aryloxy, heteroaryl, heteroaryloxy, heterocyclic, heterocyclooxy, hydroxyamino, alkoxyamino, nitro, -SO-alkyl, -SO-substituted alkyl, -SO-aryl, -SO-heteroaryl, $-SO_2$-alkyl, $-SO_2$-substituted alkyl, $-SO_2$-aryl and $-SO_2$-heteroaryl. Such heterocyclic groups can have a single ring or multiple condensed rings. Preferred heterocyclics include morpholino, piperidinyl, and the like.

Examples of nitrogen heteroaryls and heterocycles include, but are not limited to, pyrrole, thiophene, furan, imidazole, pyrazole, pyridine, pyrazine, pyrimidine, pyridazine, indolizine, isoindole, indole, indazole, purine, quinolizine, isoquinoline, quinoline, phthalazine, naphthylpyridine, quinoxaline, quinazoline, cinnoline, pteridine, carbazole, carboline, phenanthridine, acridine, phenanthroline, isothiazole, phenazine, isoxazole, phenoxazine, phenothiazine, imidazolidine, imidazoline, pyrrolidine, piperidine, piperazine, indoline, morpholine, tetrahydrofuranyl, tetrahydrothiophene, and the like as well as N-alkoxy-nitrogen containing heterocycles.

The term " heterocyclooxy " refers to the group heterocyclic-O-.

The term " thioheterocyclooxy " refers to the group heterocyclic-S-.

The term " heterocyclene " refers to the diradical group formed from a heterocycle, as defined herein, and is exemplified by the groups 2,6-morpholino, 2,5-morpholino and the like.

"Heterocycloamino" means a saturated monovalent cyclic group of 4 to 8 ring atoms, wherein at least one ring atom is N and optionally contains one or two additional ring heteroatoms selected from the group consisting of N, O, or S(O)n (where n is an integer from 0 to 2), the remaining ring atoms being C, where one or two C atoms may optionally be replaced by a carbonyl group. The

heterocycloamino ring may be fused to a cycloalkyl, aryl or heteroaryl ring, and it may be optionally substituted with one or more substituents, preferably one or two substituents, selected from alkyl, substituted alkyl, cycloalkyl, aryl, aralkyl, heteroaryl, heteroaralkyl, halo, cyano, acyl, amino, substituted amino, acylamino, -OR (where R is hydrogen, alkyl, alkenyl, cycloalkyl, acyl, aryl, heteroaryl, aralkyl, or heteroaralkyl), or -S(O)nR [where n is an integer from 0 to 2 and R is hydrogen (provided that n is 0), alkyl, alkenyl, cycloalkyl, amino, heterocyclo, aryl, heteroaryl, aralkyl, or heteroaralkyl]. More specifically the term heterocycloamino includes, but is not limited to, pyrrolidino, piperidino, morpholino, piperazino, indolino, or thiomorpholino, and the derivatives thereof.

The term " oxyacylamino " or "aminocarbonyloxy" refers to the group -OC(O)NRR where each R is independently hydrogen, alkyl, substituted alkyl, aryl, heteroaryl, or heterocyclic wherein alkyl, substituted alkyl, aryl, heteroaryl and heterocyclic are as defined herein.

The term " spiro-attached cycloalkyl group " refers to a cycloalkyl group attached to another ring via one carbon atom common to both rings.

The term "thiol" refers to the group -SH.

The term "thioalkoxy" or "alkylthio" refers to the group -S-alkyl.

The term "substituted thioalkoxy" refers to the group -S-substituted alkyl.

The term "thioaryloxy" refers to the group aryl-S- wherein the aryl group is as defined above including optionally substituted aryl groups also defined above.

The term "thioheteroaryloxy" refers to the group heteroaryl-S- wherein the heteroaryl group is as defined above including optionally substituted aryl groups as also defined above.

As to any of the above groups which contain one or more substituents, it is understood, of course, that such groups do not contain any substitution or substitution patterns which are sterically impractical and/or synthetically non-feasible. In addition, the compounds of this invention include all stereochemical isomers arising from the substitution of these compounds.

The term "pharmaceutically-acceptable salt" refers to salts which retain the biological effectiveness and properties of the multibinding compounds of this invention and which are not biologically or otherwise undesirable. In many cases, the multibinding compounds of this invention are capable of forming acid and/or base salts by virtue of the presence of amino and/or carboxyl groups or groups similar thereto.

Pharmaceutically-acceptable base addition salts can be prepared from inorganic and organic bases. Salts derived from inorganic bases, include by way of example only, sodium, potassium, lithium, ammonium, calcium and magnesium salts. Salts derived from organic bases include, but are not limited to, salts of primary, secondary and tertiary amines, such as alkyl amines, dialkyl amines, trialkyl amines, substituted alkyl amines, di(substituted alkyl) amines, tri(substituted alkyl) amines, alkenyl amines, dialkenyl amines, trialkenyl amines, substituted alkenyl amines, di(substituted alkenyl) amines, tri(substituted alkenyl) amines, cycloalkyl amines, di(cycloalkyl) amines, tri(cycloalkyl) amines, substituted cycloalkyl amines, disubstituted cycloalkyl amine, trisubstituted cycloalkyl amines, cycloalkenyl amines, di(cycloalkenyl) amines, tri(cycloalkenyl) amines, substituted cycloalkenyl amines, disubstituted cycloalkenyl amine, trisubstituted cycloalkenyl amines, aryl amines, diaryl amines, triaryl amines, heteroaryl amines, diheteroaryl amines, triheteroaryl amines, heterocyclic amines, diheterocyclic amines, triheterocyclic amines, mixed di- and tri-amines where at least two of the substituents on the amine are different and are selected from the group consisting of alkyl, substituted alkyl, alkenyl, substituted alkenyl, cycloalkyl, substituted cycloalkyl, cycloalkenyl, substituted cycloalkenyl, aryl, heteroaryl, heterocyclic, and the like. Also included are amines where the two or three substituents, together with the amino nitrogen, form a heterocyclic or heteroaryl group. Examples of suitable amines include, by way of example only, isopropylamine, trimethyl amine, diethyl amine, tri(*iso*-propyl) amine, tri(*n*-propyl) amine, ethanolamine, 2-dimethylaminoethanol, tromethamine, lysine, arginine, histidine, caffeine, procaine, hydrabamine, choline, betaine, ethylenediamine,

glucosamine, N-alkylglucamines, theobromine, purines, piperazine, piperidine, morpholine, N-ethylpiperidine, and the like. It should also be understood that other carboxylic acid derivatives would be useful in the practice of this invention, for example, carboxylic acid amides, including carboxamides, lower alkyl carboxamides, dialkyl carboxamides, and the like.

Pharmaceutically acceptable acid addition salts may be prepared from inorganic and organic acids. Salts derived from inorganic acids include hydrochloric acid, hydrobromic acid, sulfuric acid, nitric acid, phosphoric acid, and the like. Salts derived from organic acids include acetic acid, propionic acid, glycolic acid, pyruvic acid, oxalic acid, malic acid, malonic acid, succinic acid, maleic acid, fumaric acid, tartaric acid, citric acid, benzoic acid, cinnamic acid, mandelic acid, methanesulfonic acid, ethanesulfonic acid, *p*-toluene-sulfonic acid, salicylic acid, and the like.

The term " pharmaceutically-acceptable cation " refers to the cation of a pharmaceutically-acceptable salt.

The term "library" refers to at least 3, preferably from 10^2 to 10^9 and more preferably from 10^2 to 10^4 multimeric compounds. Preferably, these compounds are prepared as a multiplicity of compounds in a single solution or reaction mixture which permits facile synthesis thereof. In one embodiment, the library of multimeric compounds can be directly assayed for multibinding properties. In another embodiment, each member of the library of multimeric compounds is first isolated and, optionally, characterized. This member is then assayed,for multibinding properties.

The term "collection" refers to a set of multimeric compounds which are prepared either sequentially or concurrently (e.g., combinatorially). The collection comprises at least 2 members; preferably from 2 to 10^9 members and still more preferably from 10 to 10^4 members.

The term "multimeric compound" refers to compounds comprising from 2 to 10 ligands covalently connected through at least one linker which compounds may or may not possess multibinding properties (as defined herein).

The term “pseudohalide” refers to functional groups which react in displacement reactions in a manner similar to a halogen. Such functional groups include, by way of example, mesyl, tosyl, azido and cyano groups.

The term "protecting group" or "blocking group" refers to any group which when bound to one or more hydroxyl, thiol, amino or carboxyl groups of the compounds (including intermediates thereof) prevents reactions from occurring at these groups and which protecting group can be removed by conventional chemical or enzymatic steps to reestablish the hydroxyl, thiol, amino or carboxyl group. The particular removable blocking group employed is not critical and preferred removable hydroxyl blocking groups include conventional substituents such as allyl, benzyl, acetyl, chloroacetyl, thiobenzyl, benzylidine, phenacyl, t-butyl-diphenylsilyl and any other group that can be introduced chemically onto a hydroxyl functionality and later selectively removed either by chemical or enzymatic methods in mild conditions compatible with the nature of the product. Preferred removable thiol blocking groups include disulfide groups, acyl groups, benzyl groups, and the like. Preferred removable amino blocking groups include conventional substituents such as t-butyoxycarbonyl (t-BOC), benzyloxycarbonyl (CBZ), fluorenylmethoxy-carbonyl (FMOC), allyloxycarbonyl (ALOC), and the like which can be removed by conventional conditions compatible with the nature of the product. Preferred carboxyl protecting groups include esters such as methyl, ethyl, propyl, *t*-butyl etc. which can be removed by mild conditions compatible with the nature of the product.

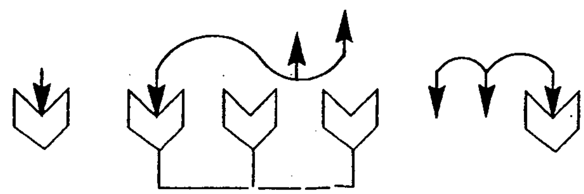
The term "optional" or "optionally" means that the subsequently described event, circumstance or substituent may or may not occur, and that the description includes instances where said event or circumstance occurs and instances where it does not.

The term "ligand" as used herein denotes a compound that is a muscarinic receptor antagonist. The specific region or regions of the ligand that is (are) recognized by the receptor is designated as the "ligand domain". A ligand may be either capable of binding to the receptor by itself, or may require the presence of

one or more non-ligand components for binding (e.g., Ca^{+2}, Mg^{+2} or a water molecule is required for the binding of a ligand to various ligand binding sites). Examples of ligands useful in this invention are described herein. Those skilled in the art will appreciate that portions of the ligand structure that are not essential for specific molecular recognition and binding activity may be varied substantially, replaced or substituted with unrelated structures (for example, with ancillary groups as defined below) and, in some cases, omitted entirely without affecting the binding interaction. The primary requirement for a ligand is that it has a ligand domain as defined above. It is understood that the term ligand is not intended to be limited to compounds known to be useful in binding to muscarinic receptor (e.g., known drugs). Those skilled in the art will understand that the term ligand can equally apply to a molecule that is not normally associated with receptor binding properties. In addition, it should be noted that ligands that exhibit marginal activity or lack useful activity as monomers can be highly active as multivalent compounds because of the benefits conferred by multivalency.

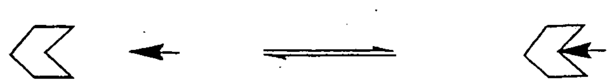
The term "multibinding compound or agent" refers to a compound that is capable of multivalency, as defined below, and which has 2-10 ligands covalently bound to one or more linkers which may be the same or different. Multibinding compounds provide a biological and/or therapeutic effect greater than the aggregate of unlinked ligands equivalent thereto which are made available for binding. That is to say that the biological and/or therapeutic effect of the ligands attached to the multibinding compound is greater than that achieved by the same amount of unlinked ligands made available for binding to the ligand binding sites (receptors). The phrase "increased biological or therapeutic effect" includes, for example: increased affinity, increased selectivity for target, increased specificity for target, increased potency, increased efficacy, decreased toxicity, improved duration of activity or action, decreased side effects, increased therapeutic index, improved bioavailibity, improved pharmacokinetics, improved activity spectrum, and the like. The multibinding compounds of this invention will exhibit at least one and preferably more than one of the above-mentioned affects.

The term "univalency" as used herein refers to a single binding interaction between one ligand as defined herein with one ligand binding site as defined herein. It should be noted that a compound having multiple copies of a ligand (or ligands) exhibit univalency when only one ligand is interacting with a ligand binding site. Examples of univalent interactions are depicted below.



The term "multivalency" as used herein refers to the concurrent binding of from 2 to 10 linked ligands (which may be the same or different) and two or more corresponding receptors (ligand binding sites) on one or more receptors which may be the same or different.

For example, two ligands connected through a linker that bind concurrently to two ligand binding sites would be considered as bivalency; three ligands thus connected would be an example of trivalency. An example of trivalent binding, illustrating a multibinding compound bearing three ligands versus a monovalent binding interaction, is shown below:



univalent interaction

trivalent interaction

It should be understood that all compounds that contain multiple copies of a ligand attached to a linker or to linkers do not necessarily exhibit the phenomena of multivalency, i.e., that the biological and/or therapeutic effect of the multibinding agent is greater than the sum of the aggregate of unlinked ligands made available for binding to the ligand binding site (receptor). For multivalency to occur, the ligands that are connected by a linker or linkers have to be presented to their ligand binding sites by the linker(s) in a specific manner in order to bring about the desired ligand-orienting result, and thus produce a multibinding event.

The term "potency" refers to the minimum concentration at which a ligand is able to achieve a desirable biological or therapeutic effect. The potency of a ligand is typically proportional to its affinity for its ligand binding site. In some cases, the potency may be non-linearly correlated with its affinity. In comparing the potency of two drugs, e.g., a multibinding agent and the aggregate of its unlinked ligand, the dose-response curve of each is determined under identical test conditions (e.g., in an *in vitro* or *in vivo* assay, in an appropriate animal model). The finding that the multbinding agent produces an equivalent biological or therapeutic effect at a lower concentration than the aggregate unlinked ligand is indicative of enhanced potency.

The term "selectivity" or "specificity" is a measure of the binding preferences of a ligand for different ligand binding sites (receptors). The selectivity of a ligand with respect to its target ligand binding site relative to another ligand binding site is given by the ratio of the respective values of K_d (i.e., the dissociation constants for each ligand-receptor complex) or, in cases where a biological effect is

observed below the K_d, the ratio of the respective EC_{50}'s (i.e., the concentrations that produce 50% of the maximum response for the ligand interacting with the two distinct ligand binding sites (receptors)).

The term "ligand binding site" denotes the site on the muscarinic receptor that recognizes a ligand domain and provides a binding partner for the ligand. The ligand binding site may be defined by monomeric or multimeric structures. This interaction may be capable of producing a unique biological effect, for example, agonism, antagonism, modulatory effects, may maintain an ongoing biological event, and the like.

It should be recognized that the ligand binding sites of the receptor that participate in biological multivalent binding interactions are constrained to varying degrees by their intra- and inter-molecular associations (e.g., such macromolecular structures may be covalently joined to a single structure, noncovalently associated in a multimeric structure, embedded in a membrane or polymeric matrix, and so on) and therefore have less translational and rotational freedom than if the same structures were present as monomers in solution.

The terms "agonism" and "antagonism" are well known in the art. The term "modulatory effect" refers to the ability of the ligand to change the activity of an agonist or antagonist through binding to a ligand binding site.

The term "allosteric modulator" as used herein denotes a compound that can regulate the activity of a muscarinic receptor. The allosteric modulator can regulate the activity of a muscarinic receptor in several ways i.e., by increasing the affinity of a muscarinic receptor for its antagonists (*see*., Nedoma, J. S. et al., *Synaptic Transmitters and Receptors* (S. Tucek, ed.) Academia, Prague/Wiley, Chichester, **1987**, 108-112; and Tucek, S. et al., *Mol. Pharmacol.* **1990**, 38:674-680; Dong, G.Z. et al, *J. Pharmacol. Exp. Ther.* **1995**, 274:378-384; Dong, G.Z. et al., *Biomed. Res.* **1995**, 16:327-335; Proska, J. and Tucek, S., *Mol. Pharmacol.* **1995**, 48:696-702; and Proska, J. and Tucek, S., *Eur. J. of Pharmacol.* **1996**, 201-205) or decreasing the affinity of a muscarinic receptor for its agonists (*see*., Clark, A.L. and Mitchelson, F., *Br. J. Pharmacol.* **1976**, 58:323-331; Christopoulos, A. and

Mitchelson, F., *Mol. Pharmacol.* **1994**, 46:105-114; and Tucek S. and Proska, J., *TiPS.* **1995**, Vol. (16), 205-212). It can also regulate the a muscarinic receptor's activity by effecting the association or dissociation of a muscarinic receptor agonist or antagonist as described in Trankle, C. et al., *Mol. Pharmacol.* **1998**, 53:304-312; and Holzgrabe, U. and Mohr, K., *DDT.* **1998**, Vol. 3. No. 5. 214-222. Compounds that effect the affinity of muscarinic receptors for their natural ligand are well known in the art. For example, gallamine inhibits the binding of [3H]-(-)-N-methylscopolamine and other specific ligands to muscarinic receptors (*see.*, Fryer, A.D and El-Fakahany, E.D., **1998**, *Membrane Biochem.*, 8, 122; and Jacoby, E.E., et al. **1993**, *J. Clin. Invest.*, 91, 1314).

The term "inert organic solvent" or "inert organic solvent" means a solvent which is inert under the conditions of the reaction being described in conjunction therewith including, by way of example only, benzene, toluene, acetonitrile, tetrahydrofuran, dimethylformamide, chloroform, methylene chloride, diethyl ether, ethyl acetate, acetone, methylethyl ketone, methanol, ethanol, propanol, isopropanol, *t*-butanol, dioxane, pyridine, and the like. Unless specified to the contrary, the solvents used in the reactions described herein are inert solvents.

The term "treatment" refers to any treatment of a pathologic condition in a mammal, particularly a human, and includes:

(i) preventing the pathologic condition from occurring in a subject which may be predisposed to the condition but has not yet been diagnosed with the condition and, accordingly, the treatment constitutes prophylactic treatment for the disease condition;

(ii) inhibiting the pathologic condition, i.e., arresting its development;

(iii) relieving the pathologic condition, i.e., causing regression of the pathologic condition; or

(iv) relieving the conditions mediated by the pathologic condition.

The term "pathologic condition which is modulated by treatment with a ligand" covers all disease states (i.e., pathologic conditions) which are generally acknowledged in the art to be usefully treated with a ligand for the muscarinic

receptors in general, and those disease states which have been found to be usefully treated by a specific multibinding compound of our invention. Such disease states include, by way of example only, the treatment of a mammal afflicted with chronic obstructive pulmonary disease, chronic bronchitis, irritable bowel syndrome, urinary incontinence, and the like.

The term "therapeutically effective amount" refers to that amount of multibinding compound which is sufficient to effect treatment, as defined above, when administered to a mammal in need of such treatment. The therapeutically effective amount will vary depending upon the subject and disease condition being treated, the weight and age of the subject, the severity of the disease condition, the manner of administration and the like, which can readily be determined by one of ordinary skill in the art.

The term "linker", identified where appropriate by the symbol 'X' refers to a group or groups that covalently attaches from 2 to 10 ligands (as identified above) in a manner that provides for a compound capable of multivalency. Among other features, the linker is a ligand-orienting entity that permits attachment of multiple copies of a ligand (which may be the same or different) thereto. In some cases, the linker may itself be biologically active. Additionally, the linker can be either a chiral or achiral molecule. The term "linker" does not, however, extend to cover solid inert supports such as beads, glass particles, fibers, and the like. But it is understood that the multibinding compounds of this invention can be attached to a solid support if desired. For example, such attachment to solid supports can be made for use in separation and purification processes and similar applications.

The extent to which multivalent binding is realized depends upon the efficiency with which the linker or linkers that joins the ligands presents these ligands to the array of available ligand binding sites. Beyond presenting these ligands for multivalent interactions with ligand binding sites, the linker or linkers spatially constrains these interactions to occur within dimensions defined by the linker or linkers. Thus, the structural features of the linker (valency, geometry,

orientation, size, flexibility, chemical composition, etc.) are features of multibinding agents that play an important role in determining their activities.

The linkers used in this invention are selected to allow multivalent binding of ligands to the ligand binding sites of a muscarinic receptor, whether such sites are located interiorly, both interiorly and on the periphery of the enzyme structure, or at any intermediate position thereof.

"Pro-drugs" means any compound which releases an active parent drug according to Formula (I) in vivo when such prodrug is administered to a mammalian subject. Prodrugs of a compound of Formula (I) are prepared by modifying functional groups present in the compound of Formula (I) in such a way that the modifications may be cleaved in vivo to release the parent compound. Prodrugs include compounds of Formula (I) wherein a hydroxy, amino, or sulfhydryl group in compound (I) is bonded to any group that may be cleaved in vivo to regenerate the free hydroxyl, amino, or sulfhydryl group, respectively. Examples of prodrugs include, but are not limited to esters (e.g., acetate, formate, and benzoate derivatives), carbamates (e.g., N,N-dimethylaminocarbonyl) of hydroxy functional groups in compounds of Formula (I), and the like.

PREFERRED EMBODIMENTS

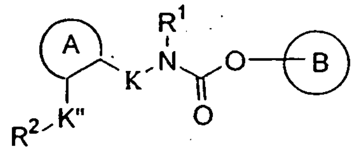
While the broadest definition of this invention is set forth in the Summary of the Invention, certain compounds of Formula (I) are preferred.

(A) A preferred group is a bivalent multibinding compound of Formula (I) shown below:

$$L — X — L$$

Within this group (A), a more preferred group of compounds is that wherein both the ligands are muscarinic receptor antagonists and are selected from the group consisting of:

(1) a compound of formula (a):



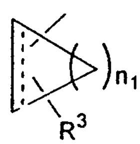
(a)

wherein:

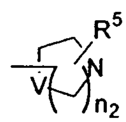
A is a phenyl or a pyridine ring;

R^1 is hydrogen or alkyl, preferably hydrogen, methyl, or ethyl, more preferably hydrogen;

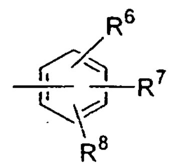
R^2 is selected from a group consisting of (i), (ii), (iii), or "Het":



(i)



(ii)



(iii)

, or "Het"

wherein:

----- is an optional double bond;

n_1 is 3 or 4;

n_2 is 1 or 2;

V is -CH- or -NR^4- (wherein R^4 is hydrogen, alkyl, substituted alkyl, aryl, or heteroaryl), preferably -CH-;

"Het" is a heteroaryl ring, preferably pyrrolyl, pyridinyl, or imidazolyl which optionally attaches the ligand to a linker;

R^3 is hydrogen or alkyl, preferably hydrogen or methyl, more preferably hydrogen;

R^5 is hydrogen, alkyl, aryl, aralkyl, heteroaralkyl, or a covalent bond attaching the ligand to a linker, preferably hydrogen, methyl, phenyl optionally substituted with alkyl, alkoxy, halo, hydroxy, carboxy, or amino, benzyl optionally substituted with alkyl, alkoxy, halo, hydroxy, carboxy, or amino or a covalent bond

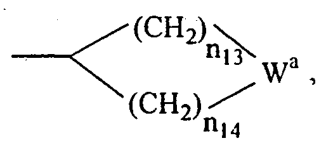
attaching the ligand to a linker, more preferably hydrogen or a covalent bond attaching the ligand to a linker;

R^6, R^7, and R^8 are, independently of each other, hydrogen, halo, hydroxy, alkoxy, haloalkoxy, carboxy, alkoxycarbonyl, alkyl optionally substituted with one, two or three substituents selected from halo, hydroxy, carboxy, alkoxycarbonyl, alkylthio, alkylsulfonyl, amino, or substituted amino, or a covalent bond attaching the ligand to a linker, preferably R^6, R^7, and R^8 are, independently of each other, hydrogen, alkyl, nitro, hydroxy, or amino, or a covalent bond attaching the ligand to a linker, most preferably R^6, R^7, and R^8 are hydrogen or one of R^6, R^7, and R^8 attaches the ligand to a linker;

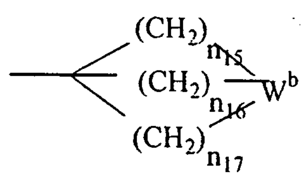
K is a bond or an alkylene group, preferably a single bond or a methylene group;

K" is a bond, -C(O)-, $-S(O)_{n4}-$ (where n_4 is an integer of from 0 to 2), or an alkylene group optionally substituted with a hydroxyl group, preferably a single bond or a methylene group; and

B is a heterocycloamino group which optionally attaches the ligand to a linker, preferably B is a group selected from a group consisting of:

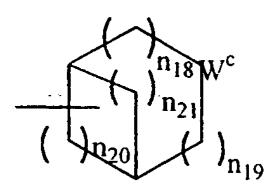


(j)



(k)

or



(l)

wherein:

n_{13} and n_{14} are, independently of each other, an integer of from 1 to 4 provided that $n_{13}+n_{14}$ are integer of from 3 to 5;

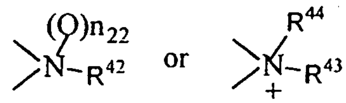
n_{15} and n_{17} are, independently of each other, an integer of from 1 to 4 provided that $n_{15}+n_{17}$ are integer of from 3 to 5;

n_{16} is an integer of from 1 to 3 provided that $n_{15} + n_{16}$ are an integer of from 3 to 5;

n_{18}, n_{19} and n_{20} are, independently of each other, an integer of from 0 to 3 provided that $n_{18}+n_{19}+n_{20}$ are 2 or 3;

n_{21} is an integer of from 1 to 3;

W^a and W^c are, independently of each other,:



where n_{22} is 0 or 1;

R^{42} and R^{43} are, independently of each other, hydrogen, alkyl, alkenyl, alkynyl, cycloalkylalkyl, aralkyl, or heterocyclylalkyl or a covalent bond attaching the ligand to a linker;

R^{44} is alkyl, alkenyl or alkynyl; and

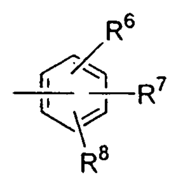
W^b is $-N(O)n_{23}$ or $-N^+-R^{45}$ where n_{23} is 0 or 1, and R^{45} is alkyl, alkenyl, alkynyl, or aralkyl, or a covalent bond attaching the ligand to a linker;

provided that one of the R^5, R^6, R^7, R^8, and the heterocycloamino group attaches the ligand to a linker.

Within this group (1) a more preferred group an even more preferred group of compounds is that wherein:

A is a phenyl;

R^2 is a group of formula (iii)



(iii)

wherein R^6, R^7 and R^8 are either hydrogen or one of R^6, R^7 and R^8 optionally attaches the ligand to a linker and the others are hydrogen;

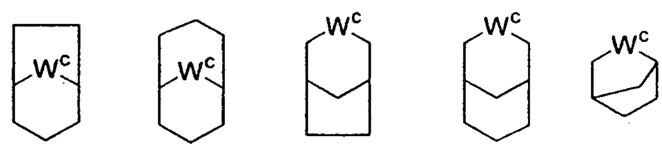
K and K" are bond; and

B is:

(a) pyrrolidine, piperidine, or hexahydroazepine optionally atttaching the ligand to a linker, preferably piperidin-4-yl wherein the nitrogen at the 1 position optionally attaches the ligand to a linker;

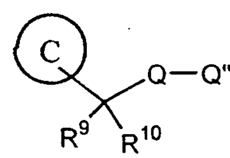
(b) quinuclidine, 1-azabicyclo[2.2.1]heptyl, or 1-azabicyclo[3.2.1]octyl optionally attaching the ligand to a linker wherein a bridge head carbon atom or a carbon atom adjacent thereto is the binding position with the oxygen atom; preferably quinuclidin-3-yl, quinuclidin-4-yl wherein the nitrogen optionally attaches the ligand to a linker; or

(c) a ring represented by the following general formulae:



wherein W^c is as defined above; or

(2) a compound of formula (b):



(b)

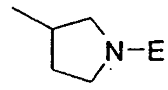
wherein:

C is an aryl ring which optionally attaches the ligand to a linker;

R^9 is hydrogen, hydroxy, cyano, aminocarbonyl, alkyl substituted with one, two or three substituents selected from halo, hydroxy, carboxy, alkoxycarbonyl, alkylthio, alkylsulfonyl, amino, substituted amino, or a covalent bond attaching the ligand to a linker;

R^{10} is hydrogen, aryl, heteroaryl, alkyl substituted with one, two or three substituents selected from halo, hydroxy, carboxy, alkoxycarbonyl, alkylthio, alkylsulfonyl, amino, substituted amino, or a covalent bond attaching the ligand to a linker; and

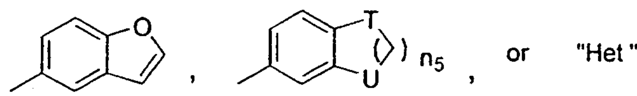
when Q is a single bond then Q" is a group of formula (iv):



(iv)

where:

E is hydrogen, a covalent bond attaching the ligand to a linker, or $-CH_2-W-R^{11}$ wherein W is a single bond or alkylene wherein one of the carbon atoms may optionally be replaced by -O-, -S-, or $-NR^a-$ wherein R^a is hydrogen or alkyl; and R^{11} is a group of formula (v), (vi) or "Het":



(v) (vi)

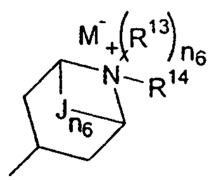
wherein:

T and U are independently of each other -O- or $-CH_2-$;

n_5 is an integer of from 1 to 3; and

"Het" is heteroaryl; and

when Q is -NHC(O)O- then Q" is a group of formula (viii)



(viii)

wherein n_6 is 0 or 1;

R^{13} is alkyl or a covalent bond attaching the ligand to a linker; and

R^{14} is hydrogen, alkyl, or a covalent bond attaching the ligand to a linker;

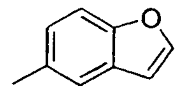
Within this group (2) a more preferred group of compounds is that wherein:

when Q is a bond then:

R^9 is aminocarbonyl or a covalent bond attaching the ligand to a linker;

C and R^{10} are phenyl;

E is $-CH_2-W-R^{11}$ wherein W is $-CH_2-$ and R^{11} is a group of formula (v) or a covalent bond attaching the ligand to a linker;



(v)

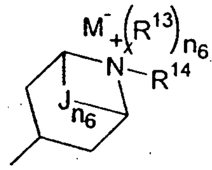
and

when Q is -NHC(O)O- then:

R^9 is hydrogen;

C and R^{10} are phenyl; and

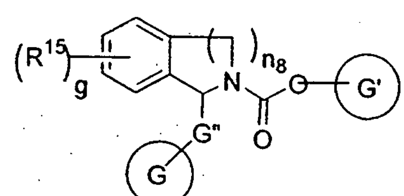
Q" is a group of formula (viii)



(viii)

wherein n_6 is 0 and R^{14} is hydrogen, alkyl, or a covalent bond attaching the ligand to a linker; or

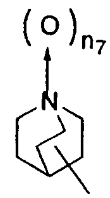
(3) a compound of formula (c):



(c)

wherein:

G' is pyrrolidine, piperidine, or



which optionally attach the ligand to a linker;

n_7 is an 0 or 1 provided that when the nitrogen atom of the quinclidine ring attaches the ligand to a linker then n_7 is 0;

n_8 is 2;

g is an integer of from 0 or 1;

R^{15} is hydrogen, halogen, nitro, cyano, hydroxy, alkoxy, carboxy, alkoxycarbonyl, acyl, thio, alkylthio, alkylsulfonyl, alkylsulfinyl, sulfonamido, alkylsulfonamido, carbamoyl, thiocarbamoyl, mono or dialkylcarbamoyl, amino, mono- or dialkylamino, methylenedioxy, ethylenedioxy, alkyl optionally substituted with one, two or three substituents selected from halo, hydroxy, carboxy, alkoxycarbonyl, alkylthio, alkylsulfonyl, amino, or substituted amino, or a covalent bond attaching the ligand to a linker, preferably hydrogen, halogen, alkyl, alkoxy, or hydroxy, or a covalent bond attaching the ligand to a linker;

G is aryl, heteroaryl, heterocyclyl, or cycloalkyl which optionally attaches the ligand to a linker, preferably phenyl, pyridin-4-yl, pyridin-3-yl, pyridin-2-yl, thiophen-2-yl, thiophen-3-yl, furan-2-yl, 4-chlorophenyl, cyclohexyl, 2-, 3-, or 4-fluorophenyl, 2-, 3-, or 4-methylphenyl, 2-, 3-, or 4-nitrophenyl, 2-, 3-, or 4-aminophenyl, 3, 4-dimethoxyphenyl, 3, 4,5 -trimethoxyphenyl, 4-ethylphenyl, 24-isopropylphenyl, 3-ethylaminophenyl, 2-methylaminophenyl, 3-dimethylaminophenyl, 4-methoxycarbonylphenyl, 4-thiolphenyl, 4-methylthiophenyl, 4-methylsulfoxidephenyl, 4-methylsulfonylphenyl, N-methylpiperidin-4-yl, pyrrol-2-yl, oxazol-2-yl, quinolin-4-yl, isoquinolin-4-yl, benzofuran-2-yl, benzothiophen-3-yl, morpholin-4-yl, piperazin-1-yl, piperidin-4-yl, dichlorophenyl, 4-aminomethylphenyl, 4-hydroxymethylphenyl, cyclopentyl which optionally link the ligand to a linker; and

G" is a single bond or an alkylene group, preferably a single bond or a methylene group.

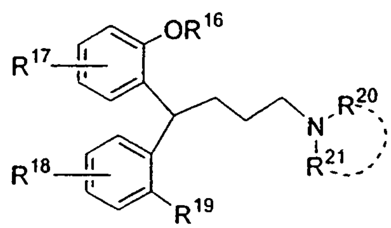
Within this group (3), a more preferred group of compounds is that wherein:

g is 0;

G is a phenyl ring which optionally attaches the ligand to a linker; and

G" is a single bond; or

(4) a compound of formula (e):



(e)

wherein:

R^{16} is alkyl or a covalent bond attaching the ligand to a linker;

R^{17}, R^{18}, and R^{19} are, independently of each other, hydrogen, alkyl, alkoxy, hydroxy or a covalent bond linking the ligand to a linker; more preferably hydrogen, methyl, methoxy, hydroxy, or a covalent bond linking the ligand to a linker;

R^{20} and R^{21} are, independently of each other, hydrogen, alkyl or a covalent bond linking the ligand to a linker; or R^{20} and R^{21} together with the nitrogen atom to which they are attached form a heterocycloamino ring which optionally attaches the ligand to a linker.

Within this group (4) a more preferred group of compounds is that wherein:

R^{16} is methyl or a covalent bond linking the ligand to a linker;

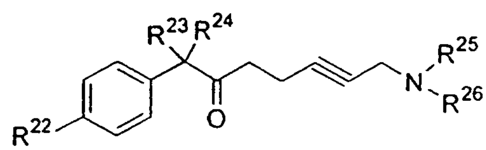
R^{17} is either meta or para to the -OR^{16} group and is hydrogen, hydroxy, or methyl or a covalent bond linking the ligand to a linker;

R^{18} is hydrogen;

R^{19} is hydrogen or hydroxy, preferably hydrogen; and

R^{20} and R^{21} are N,N-(isopropyl)amino, N-methyl-N-*tert*-butylamino, 2,2,6,6-tetramethylpiperidino, N-methyl-N-adamantylamino which optionally attaches the ligand to a linker, or one of R^{20} and R^{21} is hydrogen or alkyl and the other is a covalent bond attaching the ligand to a linker, preferably N,N-(isopropyl)amino, N-methyl-N-*tert*-butylamino, or one of R^{20} and R^{21} is hydrogen, methyl, or ethyl and the other is a covalent bond attaching the ligand to a linker; or

(5) a compound of formula (f):



(f)

wherein:

R^{22} is hydrogen or halo;

R^{23} is alkyl, cycloalkyl, aryl, heteroaryl, or heterocyclyl, or heterocyclylalkyl, preferably cyclobutyl, cyclopentyl, cyclohexyl, adamantyl, pyrrolidin-1-ylmethyl, piperidin-1-ylmethyl, piperazin-1-ylmethyl wherein the nitrogen at the 4-position of the piperazine ring is optionally substituted with a substituent selected from fluoro, hydroxy, nitro, methoxy, methyl, or trifluoromethyl, or phenyl, naphthyl, or pyridyl optionally substituted with 1-3 substituents selected from fluoro, hydroxy, nitro, methoxy, methyl, trifluoromethyl, methylcarbonyl, or amino;

R^{24} is hydroxy, halo, or a covalent bond attaching the ligand to a linker, preferably hydrogen, fluoro or a covalent bond attaching the ligand to a linker;

R^{25} and R^{26} are, independently of each other, hydrogen, alkyl, aralkyl, or a covalent bond attaching the ligand to a linker, or R^{25} and R^{26} together with the nitrogen atom to which they are attached form a heterocycloamino group which optionally attaches the ligand to a linker, preferably hydrogen, methyl, ethyl, phenylethyl, or a covalent bond attaching the ligand to a linker.

Within this group (5), a more preferred group of compounds is that wherein:

R^{22} is hydrogen or fluoro, preferably hydrogen;

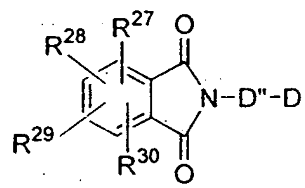
R^{23} is cyclohexyl;

R^{24} is hydroxy or a covalent bond attaching the ligand to a linker;

R^{25} and R^{26} are, independently of each other, hydrogen, methyl, ethyl, or a covalent bond attaching the ligand to a linker.

(B) Another more preferred group of compounds is that wherein one of the ligands is a muscarinic receptor antagonists selected from the groups (A)(1) to (A)(5) described above, and the other is an allosteric modulator of a muscarinic receptor said allosteric modulator is selected from the group consisting of:

(6) a compound of formula (g):



(g)

wherein:

D" is alkylene, preferably $-(CH_2)n_{43}-$ where n_{43} is an integer of from 1-10, more preferably 2-8;

D is $-NR^{31}R^{32}$, $-N^{+}(R^{33}R^{34}R^{35})M^{-}$ or $-OR^{32}$ where R^{31}, R^{33}, and R^{34} are, independently of each other, hydrogen, alkyl, or aralkyl, and R^{32} and R^{35} represent a covalent bond attaching the ligand to a linker, preferably R^{31}, R^{33}, and R^{34} are, independently of each other, hydrogen or methyl, and R^{32} and R^{35} represent a covalent bond attaching the ligand to a linker;

R^{27} is hydrogen, halo, nitro, cyano, hydroxy, alkoxy, carboxy, alkoxycarbonyl, acyl, thio, alkylthio, alkylsulfonyl, alkylsulfinyl, sulfonamido, alkylsulfonamido, carbamoyl, thiocarbamoyl, mono or dialkylcarbamoyl, amino, mono- or dialkylamino, aryl, aryloxy, arylthio, heteroaryl, heteraryloxy, heteroarylthio, heterocyclyl, heterocyclyloxy, aralkyl, heteroaralkyl, or alkyl optionally substituted with one, two or three substituents selected from halo,

hydroxy, carboxy, alkoxycarbonyl, alkylthio, alkylsulfonyl, amino, or substituted amino;

R^{28} is hydrogen, halo, nitro, cyano, hydroxy, alkoxy, carboxy, alkoxycarbonyl, acyl, thio, alkylthio, alkylsulfonyl, alkylsulfinyl, sulfonamido, alkylsulfonamido, carbamoyl, thiocarbamoyl, mono or dialkylcarbamoyl, amino, mono- or dialkylamino, or alkyl optionally substituted with one, two or three substituents selected from halo, hydroxy, carboxy, alkoxycarbonyl, alkylthio, alkylsulfonyl, amino, or substituted amino;

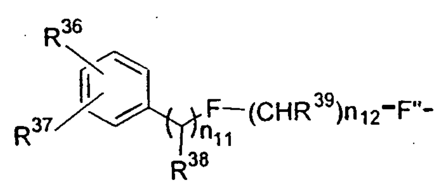
R^{29} and R^{30} are, independently of each other, hydrogen, alkyl, haloalkyl, halo, nitro, cyano, hydroxy, alkoxy, alkoxycarbonyl, acyl, thio, alkylthio, amino, mono- or dialkylamino; or

one of R^{27}, R^{28}, R^{29}, or R^{30} together with the adjacent group forms a methylenedioxy or ethylenedioxy group.

Within this group, a more preferred group of compounds is that wherein:

R^{27}, R^{28}, R^{29}, and R^{30} are hydrogen; or

(7) a compound of formula (h):



(h)

wherein:

n_{11} is an integer of from 1 to 7;

n_{12} is an integer of from 0 to 7;

F is $-NR^{40}-$, -O-, -S-, or $-CHR^{41}-$ wherein R^{40} and R^{41} are, independently of each other, hydrogen or alkyl;

F" is a covalent bond, $-OR^{43}$, $-NR^{42}R^{43}$ wherein R^{42} is hydrogen or alkyl, or $-N^{+}(R^{43}R^{44}R^{45})$ wherein R^{44} and R^{45} are alkyl, and R^{43} is a covalent bond attaching the ligand to a linker;

R^{36} is hydrogen, halo, nitro, cyano, hydroxy, alkoxy, carboxy, alkoxycarbonyl, acyl, thio, alkylthio, alkylsulfonyl, alkylsulfinyl, sulfonamido, alkylsulfonamido, carbamoyl, thiocarbamoyl, mono or dialkylcarbamoyl, amino, mono- or dialkylamino, aryl, aryloxy, arylthio, heteroaryl, heteraryloxy, heteroarylthio, heterocyclyl, heterocyclyloxy, aralkyl, heteroaralkyl, or alkyl optionally substituted with one, two or three substituents selected from halo, hydroxy, carboxy, alkoxycarbonyl, alkylthio, alkylsulfonyl, amino, or substituted amino;

R^{37} is hydrogen, halo, nitro, cyano, hydroxy, alkoxy, alkoxycarbonyl, acyl, thio, alkylthio, amino, mono- or dialkylamino, aryl, aryloxy, arylthio, heteroaryl, heteraryloxy, heteroarylthio, heterocyclyl, heterocyclyloxy, aralkyl, heteroaralkyl, or alkyl optionally substituted with one, two or three substituents selected from halo, hydroxy, carboxy, alkoxycarbonyl, alkylthio, alkylsulfonyl, amino, or substituted amino; and

R^{38} is hydrogen, alkyl, halo, hydroxy, or alkoxy.

Within this group (7), a more preferred group of compounds is that wherein:

R^{36} and R^{38} are hydrogen.

R^{37} is ortho to the -(CHR^{38})- group and is hydrogen or alkoxy, preferably methoxy;

F is -O-, -NH-, or -N(CH_3)-;

F" is methylamino, dimethylamino wherein the nitrogen atom is attached to a linker.

Within the above preferred groups A and (B), particularly preferred group of compounds is that wherein the linker, X, in the bivalent multibinding compound of Formula (I) independently has the formula:

$$-X^a-Z-(Y^a-Z)_m-Y^b-Z-X^a-$$

wherein

m is an integer of from 0 to 20;

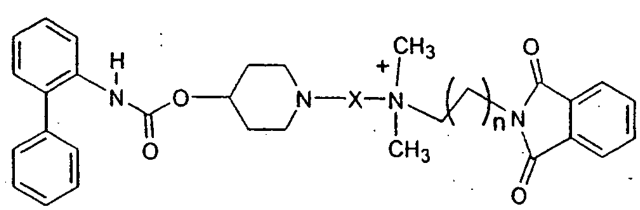
X^a at each separate occurrence is selected from the group consisting of -O-, -S-, -NR-, -C(O)-, -C(O)O-, -C(O)NR-, -C(S), -C(S)O-, -C(S)NR- or a covalent bond where R is as defined below;

Z at each separate occurrence is selected from the group consisting of alkylene, substituted alkylene, cycloalkylene, substituted cylcoalkylene, alkenylene, substituted alkenylene, alkynylene, substituted alkynylene, cycloalkenylene, substituted cycloalkenylene, arylene, heteroarylene, heterocyclene, or a covalent bond;

Y^a and Y^b at each separate occurrence are selected from the group consisting of -O-, -C(O)-, -OC(O)-, -C(O)O-, -NR-, -S(O)n-, -C(O)NR'-, -NR' C(O)-, -NR' C(O)NR'-, -NR' C(S)NR'-, -C(=NR')-NR'-, -NR'-C(=NR')-, -OC(O)-NR'-, -NR'-C(O)-O-, -N=C(X^a)-NR'-, -NR'-C(X^a)=N-,-P(O)(OR')-O-, -O-P(O)(OR')-, -S(O)$_n$CR' R"-, -S(O)$_n$-NR'-, -NR'-S(O)$_n$-, -S-S-, and a covalent bond; where *n* is 0, 1 or 2; and R, R' and R" at each separate occurrence are selected from the group consisting of hydrogen, alkyl, substituted alkyl, cycloalkyl, substituted cycloalkyl, alkenyl, substituted alkenyl, cycloalkenyl, substituted cycloalkenyl, alkynyl, substituted alkynyl, aryl, heteroaryl and heterocyclic.

Particularly preferred compounds are listed below:

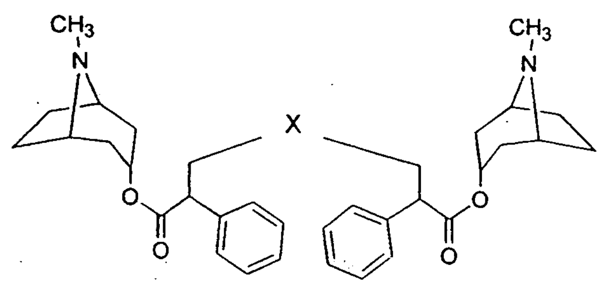
I. Compounds of Formula (I) where p is 2 and q is 1 and other groups are as defined below are:



Cpd #	X	n

1	$-(CH_2)_{10}-$	2
2	$-(CH_2)-CH(OH)-(CH_2)-$	3
3	$-(CH_2)_2-N(CH_3)-(CH_2)_2-$	1
4	$-(CH_2)-Z-(CH_2)-$ where Z is 1,3-phenylene	1
5	$-(CH_2)-Z-(CH_2)-$ where Z is 1,3-phenylene	2
6	$-(CH_2)_6-$	2

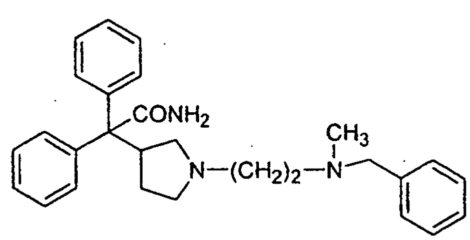
II. Compounds of Formula (I) where p is 2 and q is 1 and other groups are as defined below are:



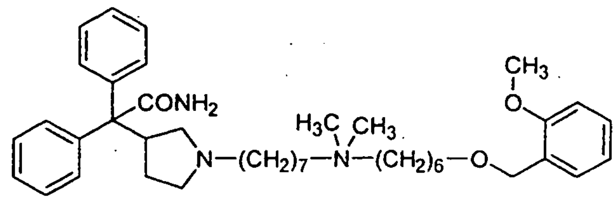
Cpd #	X
7	-O-C(O)-NH-Z-NH-C(O)-O- where Z is 1,3-phenylene

III. Other preferred compounds of Formula (I) where p is 2 and q is 1 and other groups are as shown below are:

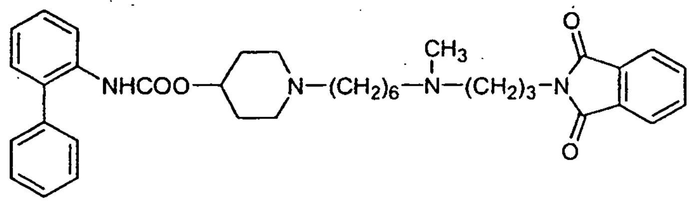
8.



9.



10.



GENERAL SYNTHETIC SCHEME

Compounds of this invention can be made by the methods depicted in the reaction schemes shown below.

The starting materials and reagents used in preparing these compounds are either available from commercial suppliers such as Aldrich Chemical Co., (Milwaukee, Wisconsin, USA), Bachem (Torrance, California, USA), Emka-Chemie, or Sigma (St. Louis, Missouri, USA) or are prepared by methods known to those skilled in the art following procedures set forth in references such as Fieser and Fieser's Reagents for Organic Synthesis, Volumes 1-15 (John Wiley and Sons, 1991); Rodd's Chemistry of Carbon Compounds, Volumes 1-5 and Supplementals (Elsevier Science Publishers, 1989), Organic Reactions, Volumes 1-40 (John Wiley and Sons, 1991), March's Advanced Organic Chemistry, (John Wiley and Sons, 4th Edition), and Larock's Comprehensive Organic Transformations (VCH Publishers Inc., 1989).

The starting materials and the intermediates of the reaction may be isolated and purified if desired using conventional techniques, including but not limited to

filtration, distillation, crystallization, chromatography, and the like. Such materials may be characterized using conventional means, including physical constants and spectral data.

Furthermore, it will be appreciated that where typical or preferred process conditions (i.e., reaction temperatures, times, mole ratios of reactants, solvents, pressures, etc.) are given, other process conditions can also be used unless otherwise stated. Optimum reaction conditions may vary with the particular reactants or solvent used, but such conditions can be determined by one skilled in the art by routine optimization procedures.

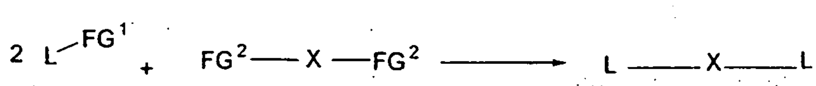
Additionally, as will be apparent to those skilled in the art, conventional protecting groups may be necessary to prevent certain functional groups from undergoing undesired reactions. The choice of a suitable protecting group for a particular functional group as well as suitable conditions for protection and deprotection are well known in the art. For example, numerous protecting groups, and their introduction and removal, are described in T. W. Greene and G. M. Wuts, *Protecting Groups in Organic Synthesis*, Second Edition, Wiley, New York, 1991, and references cited therein.

These schemes are merely illustrative of some methods by which the compounds of this invention can be synthesized, and various modifications to these schemes can be made and will be suggested to one skilled in the art having referred to this disclosure.

<u>Preparation of a multibinding compound of Formula (I)</u>

A bivalent multibinding compound of Formula (I) can be prepared by covalently attaching the ligands, L, to a linker, X, as shown in Scheme I below.

<u>Scheme I</u>



In general, a bivalent multibinding compound of Formula (I) can be prepared, as shown above, by covalently attaching the ligand, L, that is a muscarinic

receptor antagonist or a muscarinic receptor modulator to a linker, X, where FG^1 and FG^2 represent a functional group such as halo, amino, hydroxy, thio, aldehyde, ketone, carboxy, carboxy derivatives such as acid halide, ester, amido, and the like.

The ligands are covalently attached to the linker using conventional chemical techniques providing for covalent linkage of the ligand to the linker. Reaction chemistries resulting in such linkages are well known in the art and involve the use of complementary functional groups on the linker and ligand as shown in Table I below.

Table I

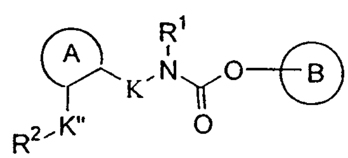
Representative Complementary Binding Chemistries

First Reactive Group	Second Reactive Group	Linkage
carboxyl	amine	amide
sulfonyl	halide amine	sulfonamide
hydroxyl	alkyl/aryl halide	ether
hydroxyl	isocyanate	urethane
amine	epoxide	β-hydroxyamine
amine	alkyl/aryl halide	alkylamine
hydroxyl	carboxyl	ester

Reaction between a carboxylic acid of either the linker or the ligand and a primary or secondary amine of the ligand or the linker in the presence of suitable, well-known activating agents such as dicyclohexylcarbodiimide, results in formation of an amide bond covalently linking the ligand to the linker; reaction between an amine group of either the linker or the ligand and a sulfonyl halide of the ligand or the linker, in the presence of a base such as triethylamine, pyridine, and the like ,results in formation of a sulfonamide bond covalently linking the ligand to the linker; and reaction between an alcohol or phenol group of either the linker or the ligand and an alkyl or aryl halide of the ligand or the linker in the presence of a base such as triethylamine, pyridine, and the like, results in formation of an ether bond covalently linking the ligand to the linker.

Any compound which inhibits a muscarinic receptor or is an allosteric modulator of a muscarinic receptor can be used as a ligand in this invention. As discussed in further detail below, numerous antagonists and allosteric modulators of muscarinic receptor are known in the art and any of these known compounds or derivatives thereof may be employed as ligands in this invention. Typically, a compound selected for use as a ligand will have at least one functional group, such as an amino, hydroxyl, thiol or carboxyl group and the like, which allows the compound to be readily coupled to the linker. Compounds having such functionality are either known in the art or can be prepared by routine modification of known compounds using conventional reagents and procedures. The patents and publications set forth below provide numerous examples of suitably functionalized muscarinic receptor antagonist, allosteric modulators and intermediates thereof which may be used as ligands in this invention. For example,

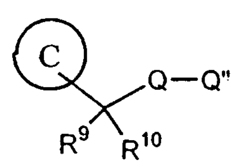
a ligand having formula (a):



(a)

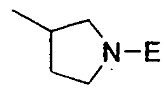
wherein A is a phenyl or pyridine ring and other groups are as defined above, can be prepared by the procedures described in EP 747.355; Naito, R. et al, *Chem. Pharm. Bull.* **1998**, 46(8), 1286.

A ligand having formula (b):



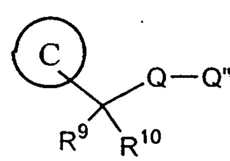
(b)

wherein the groups C and R^{10} are phenyl, R^9 is cyano or aminocarbonyl, Q is a bond, and Q" is a group of formula



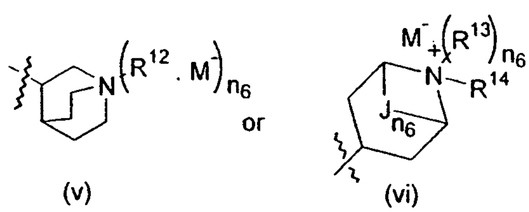
wherein E is as defined above, can be prepared by the procedures described in U.S. Patent No. 5,096,890 and *Drugs of the Future,* **1996**, 21(11), 1105. Such ligands include Darifenacin and the derivatives thereof.

A ligand having formula (b):



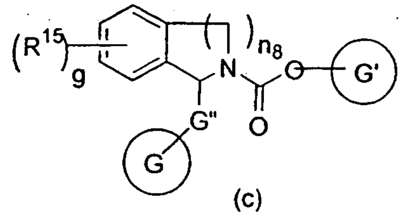
(b)

wherein C and R^{10} are phenyl, R^9 is hydrogen, Q is -NHC(O)O- and Q" is a group of formula (v) or (vi)



wherein n_6, J, R^{12}, R^{13}, and R^{14} are as defined above, can be prepared by the procedures described in U.S. Patent No. 3,505,337, EP 418 716, *Drugs of the Future*, **1997**, 22(2) 135, EP 603229, PCT Application No. WO 93/06098, Naito, R et al, *Chem. Pharm. Bull.* **1998**, 46(8), 1274, Ninomiya K et al, *Tetrahedron*, **1974**, 30, 2251 and PCT Application No. WO 92/06958. Such ligands include Tiotropium, Ipratropium, Revatropate, Atropine, YM-58790, and the derivatives thereof.

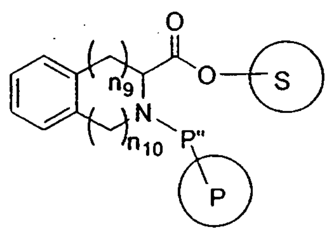
A ligand having formula (c):



(c)

wherein n_8, R^{15}, G, G', and G" are as defined above, can be prepared by the procedures described in EP 801 067. Such ligands include YM-53705, and the derivatives thereof.

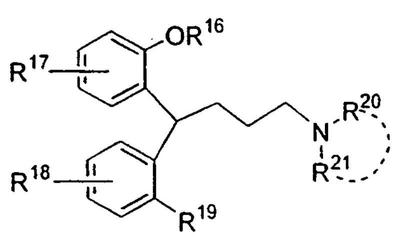
A ligand having formula (d):



(d)

wherein n^9, n^{10}, S, P and P" are as defined above, can be prepared by the procedures described in JP 258 250;

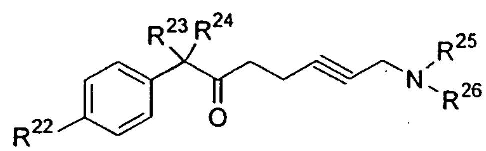
A ligand having formula (e):



(e)

wherein R^{16}-R^{21} are as defined above, can be prepared by the procedures described in EP 325 571 and *Drugs of the Future*, **1997**, 22(7), 733. Such ligands include Tolterodine and the derivatives thereof.

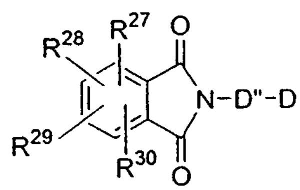
A ligand having formula (f):



(f)

wherein R^{22}-^{26} are as defined above, can be prepared by the procedures described in EP 251126. Such ligands include Oxybutynin and the derivatives thereof.

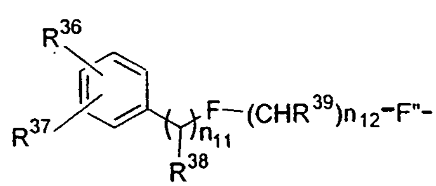
A ligand having formula (g):



(g)

wherein R^{27}-R^{30}, D and D" are as defined above, can be prepared by the procedures described in Kostenis, E. et al. *Eur. J. Med. Chem.*, **1994**, Vol. 29, 947. Such ligands include allosteric modulator W-84 and derivatives thereof.

A ligand having formula (h):



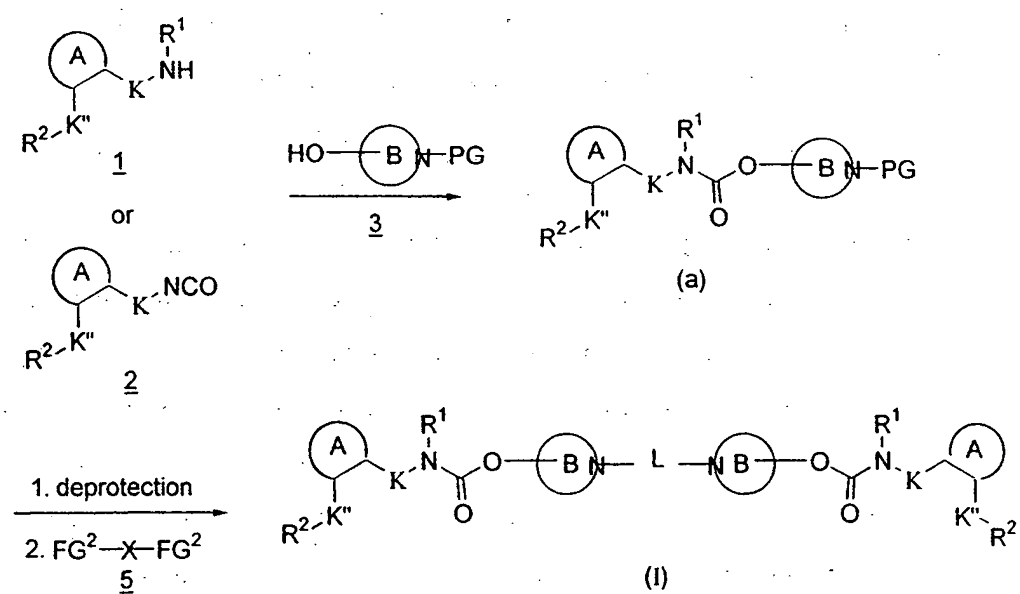
(h)

wherein n_{11}, n_{12}, F, F", and R^{36}-R^{39} are as defined above can be prepared by the procedures well known in the art e.g., Quaglia, W., et al., *IL FARMACO*, 46(3), 417-434, (1991); Melchiorre, C., et al., *J. Med. Chem.*, 32, 79-84, (1989); Minarini, A., et al., *IL FARMACO*, 46(10), 1167-1178, (1991); Alvarez, M., et al., *J. Med. Chem.*, 30, 1186-1193 (1987); and Melchiorre, C., et al., *J. Med. Chem.*, 30, 201-204, (1987).

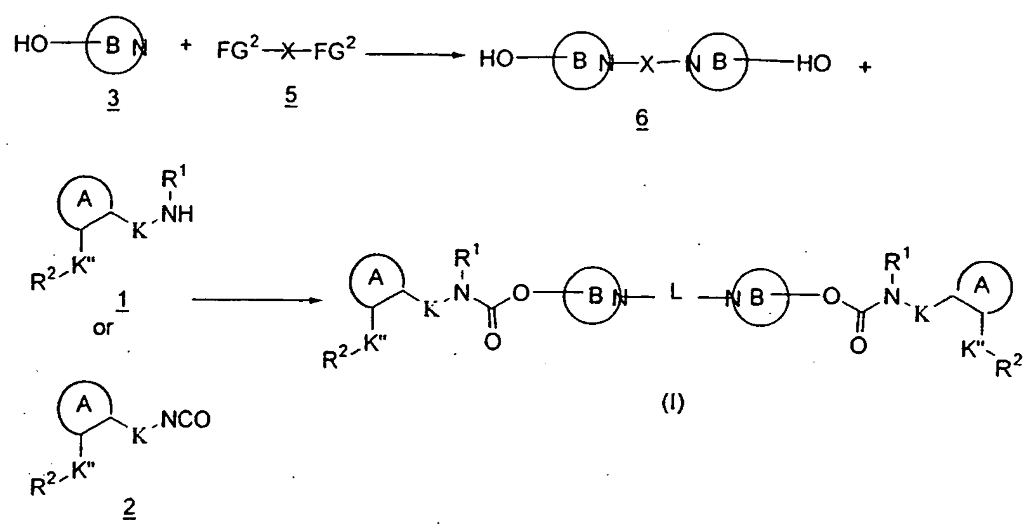
Methods (a)-(e) below illustrate synthesis of bivalent multibinding compounds of Formula (I). They are given to enable those skilled in the art to more clearly understand the present invention. They should not be considered as limiting the scope of the invention, but merely as being illustrative and representative thereof.

Methods (a) and (b) below illustrate synthesis of a bivalent compound of Formula (I) wherein the ligands are selected from a compound of formula (a).

Method(a)



Method (b)



In method (a), reaction of an amine of formula 1 or an isocycante of formula 2 with a heterocycloamino group of formula 3 where PG is a suitable amino protecting group (such as *tert*-butoxycarbonyl, benzyl, and the like) gives a compound of formula (a). The reaction is carried out in the presence of a base such as sodium hydride, sodium methoxide, and the like. Suitable solvents include inert organic organic solvents such as tetrahydrofuran, dimethylformamide, dichloromethane, and the like. Amines and isocyantes of formula 1 and 2 are commercially available or can be prepared by methods well known in the art. For example, 2-biphenylisocyanate and 2-aminobiphenyl are commercially available.

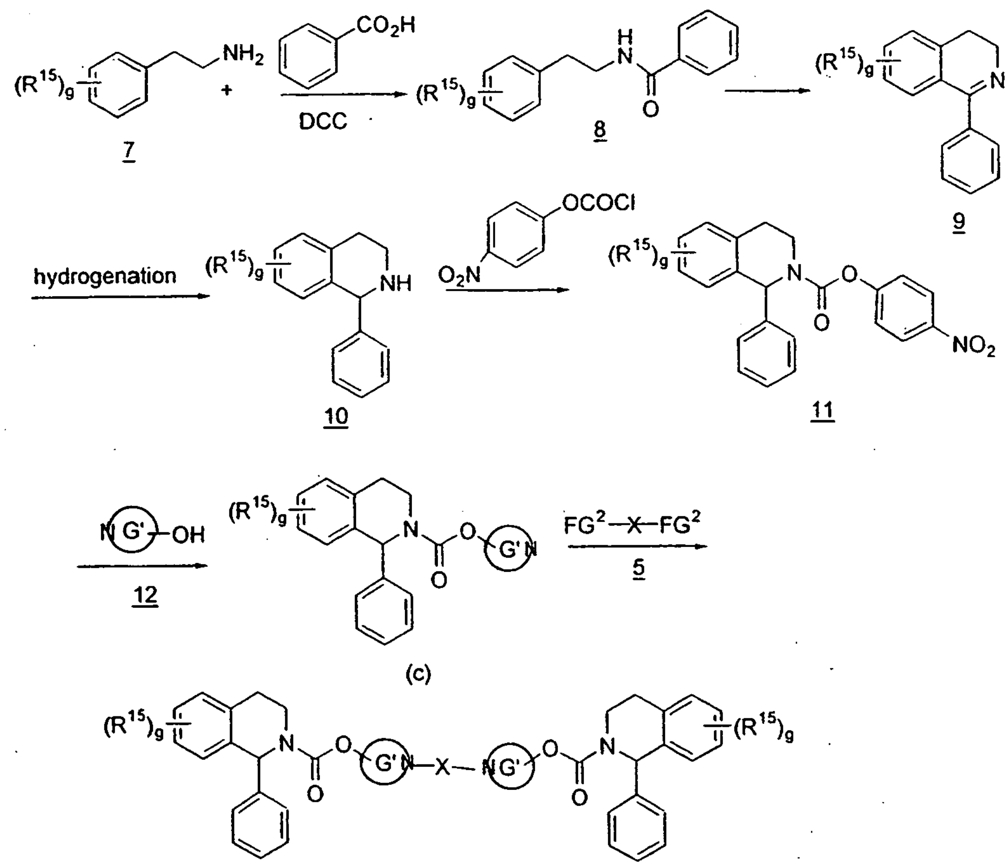
Compound (a) is then converted to a bivalent multibinding compound of Formula (I) by first removing the protecting group on the nitrogen and then reacting it with a linker of formula 5. The nature of the FG^2 group depends on the type of linker group desired. For example, if X is an alkylene chain then FG^2 would preferably be halide. If the attachement of (a) to the linker is via an amido group then FG^2 would preferably be a carboxy group or a carboxylic acid derivative such as acid chloride, ester, and the like. Compounds of formula 5 are commercially available or they can be prepared by methods well known in the art. For example, 1,2-dichloroethane, 1,2-dibromoethane, 1,2-dibromopropane, phthalic acid are

commercially available. Suitable solvents include inert organic organic solvents such as tetrahydrofuran, dimethylformamide, dichloromethane, and the like.

Alternatively, a compound of Formula (I) can be prepared as shown in Method (b) above. In this method, 2 equivalents of a heterocycloamino group of formula 3 is reacted with one equivalent of a linker of formula 5 as described previously to give a dihydroxy compound of formula 6 which is then converted to a compound of Formula (I) by reacting it with an amine 1 or an isocyanate of formula 2 as described in method (a) above.

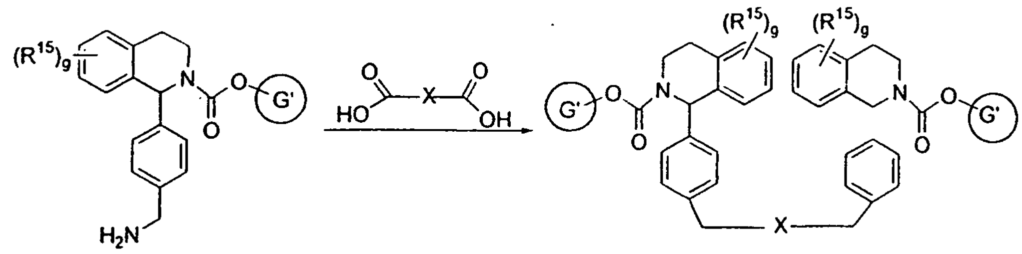
Method (c) and (d) below illustrate synthesis of a bivalent multibinding compound of Formula (I) wherein the ligands are selected from a compound of formula (c) where G is phenyl.

Method (c)



(I)

Method (d)



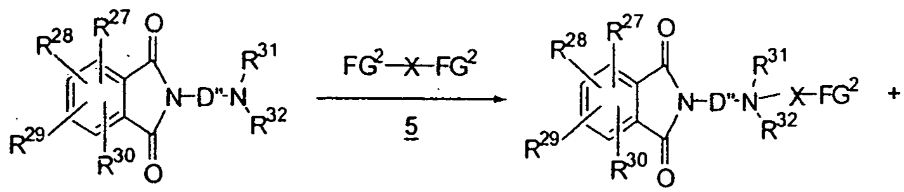
(I)

In method (c), a 2-phenylethylamine of formula 7 is condensed with benzoic acid to give an amide of formula 8. The reaction is carried out in the presence of a coupling agent such as dicyclohexylcarbodiimide, and the like. Cyclization of 8 followed by hydrogenation of the resulting imine 9 provides a tetrahydroisoquinoline of formula 10. Reaction of 10 with 4-nitrophenyl-chloroformate provides a carbamate of formula 11 which is then reacted with a hydroxyamine of formula 12 to give a compound of formula (c). Treatment of 2 equivalents of compound (c) with one equivalent of formula 5 provides a bivalent multibinding compound of Formula (I).

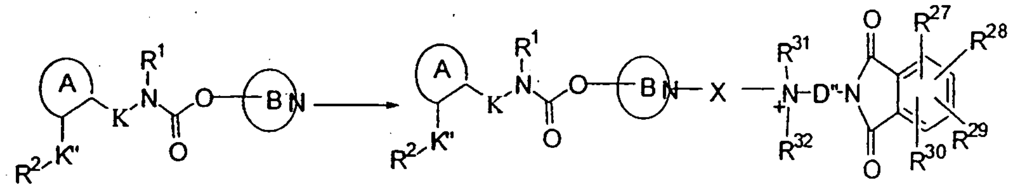
Method (d) illustrates synthesis of a bivalent multibinding compound of Formula (I) with a different point of attachement to the linker.

Method (e) below illustrate synthesis of a bivalent multibinding compound of Formula (I) wherein the one of the ligand is selected from a a muscarinic receptor antagonist ((selected from compound of formula (a)) and the other is a modulator of a muscarinic receptor ((selected from a compound of formula (g)).

Method (e)



(g) 13



(a) (I)

A bivalent multibinding compound of Formula (I) wherein the one of the ligands is selected from a compound of formula (a) (a muscarinic receptor antagonist) and the other is selected from a compound of formula (g) (a modulator of a muscarinic receptor) can be prepared by first reacting one equivivalent of a compound of (g) where D is -$NR^{31}R^{32}$ (where R^{31} and R^{32} are as defined above) with a linking compound of formula 5 to give a compound of formula 13. Compound 13 is then reacted with a compound of formula (a) to give a bivalent multibinding compound of Formula (I). A compound of formula (g) can be prepared from commercially available phthalimides. For example, a compound of formula (g) where D" is propyl and D is dimethylamino group can be prepared by reacting commercially available N-(3-bromopropyl)phthalimide with dimethylamine.

It will be apparent to one skilled in the art that the above chemistries is not limited to preparing bivalent multibinding compounds of Formula (I) and can be used to prepare tri-, tetra-, etc., multibinding compounds of Formula (I).

The linker is attached to the ligand at a position that retains ligand domain-ligand binding site interaction and specifically which permits the ligand domain of the ligand to orient itself to bind to the ligand binding site. Such positions and

synthetic protocols for linkage are well known in the art. The term linker embraces everything that is not considered to be part of the ligand.

The relative orientation in which the ligand domains are displayed derives from the particular point or points of attachment of the ligands to the linker, and on the framework geometry. The determination of where acceptable substitutions can be made on a ligand is typically based on prior knowledge of structure-activity relationships (SAR) of the ligand and/or congeners and/or structural information about ligand-receptor complexes (e.g., X-ray crystallography, NMR, and the like). Such positions and the synthetic methods for covalent attachment are well known in the art. Following attachment to the selected linker (or attachment to a significant portion of the linker, for example 2-10 atoms of the linker), the univalent linker-ligand conjugate may be tested for retention of activity in the relevant assay.

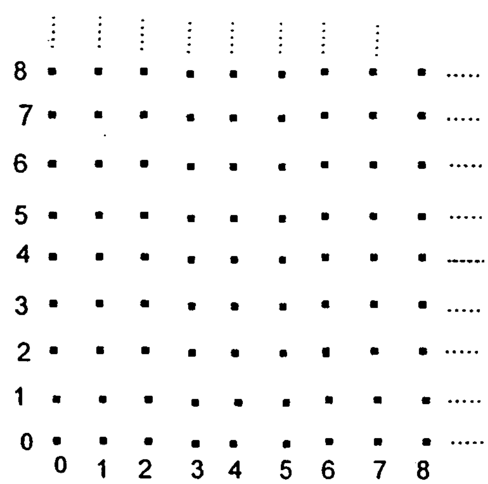
The linker, when covalently attached to multiple copies of the ligands, provides a biocompatible, substantially non-immunogenic multibinding compound. The biological activity of the multibinding compound is highly sensitive to the valency, geometry, composition, size, flexibility or rigidity, etc. of the linker and, in turn, on the overall structure of the multibinding compound, as well as the presence or absence of anionic or cationic charge, the relative hydrophobicity/hydrophilicity of the linker, and the like on the linker. Accordingly, the linker is preferably chosen to maximize the biological activity of the multibinding compound. The linker may be chosen to enhance the biological activity of the molecule. In general, the linker may be chosen from any organic molecule construct that orients two or more ligands to their ligand binding sites to permit multivalency. In this regard, the linker can be considered as a "framework" on which the ligands are arranged in order to bring about the desired ligand-orienting result, and thus produce a multibinding compound.

For example, different orientations can be achieved by including in the framework groups containing mono- or polycyclic groups, including aryl and/or heteroaryl groups, or structures incorporating one or more carbon-carbon multiple bonds (alkenyl, alkenylene, alkynyl or alkynylene groups). Other groups can also

include oligomers and polymers which are branched- or straight-chain species. In preferred embodiments, rigidity is imparted by the presence of cyclic groups (e.g., aryl, heteroaryl, cycloalkyl, heterocyclic, etc.). In other preferred embodiments, the ring is a six or ten member ring. In still further preferred embodiments, the ring is an aromatic ring such as, for example, phenyl or naphthyl.

Different hydrophobic/hydrophilic characteristics of the linker as well as the presence or absence of charged moieties can readily be controlled by the skilled artisan. For example, the hydrophobic nature of a linker derived from hexamethylene diamine ($H_2N(CH_2)_6NH_2$) or related polyamines can be modified to be substantially more hydrophilic by replacing the alkylene group with a poly(oxyalkylene) group such as found in the commercially available "Jeffamines".

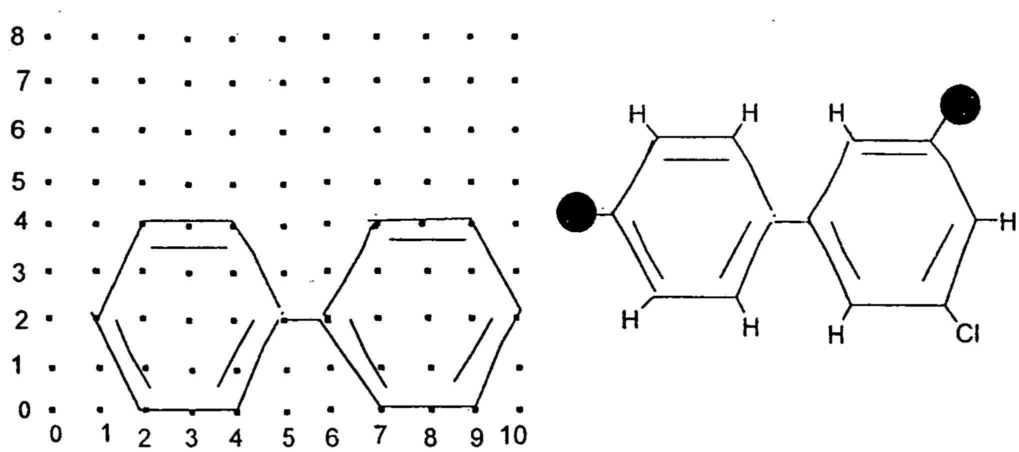
Different frameworks can be designed to provide preferred orientations of the ligands. Such frameworks may be represented by using an array of dots (as shown below) wherein each dot may potentially be an atom, such as C, O, N, S, P, H, F, Cl, Br, and F or the dot may alternatively indicate the absence of an atom at that position. To facilitate the understanding of the framework structure, the framework is illustrated as a two dimensional array in the following diagram, although clearly the framework is a three dimensional array in practice:



Each dot is either an atom, chosen from carbon, hydrogen, oxygen, nitrogen, sulfur, phosphorus, or halogen, or the dot represents a point in space (i.e., an absence of an atom). As is apparent to the skilled artisan, only certain atoms on the grid have the ability to act as an attachment point for the ligands, namely, C, O, N, S and P.

Atoms can be connected to each other via bonds (single, double or triple bonds with acceptable resonance and tautomeric forms), with regard to the usual constraints of chemical bonding. Ligands may be attached to the framework via single, double or triple bonds (with chemically acceptable tautomeric and resonance forms). Multiple ligand groups (2 to 10) can be attached to the framework such that the minimal, shortest path distance between adjacent ligand groups does not exceed 100 atoms. Preferably, the linker connections to the ligand is selected such that the maximum spatial distance between two adjacent ligands is no more than 100Å.

An example of a linker as presented by the grid is shown below for a biphenyl construct.



Nodes (1,2), (2,0), (4,4), (5,2), (4,0), (6,2), (7,4), (9,4), (10,2), (9,0), (7,0) all represent carbon atoms. Node (10,0) represents a chlorine atom. All other nodes (or dots) are points in space (i.e., represent an absence of atoms).

Nodes (1,2) and (9,4) are attachment points. Hydrogen atoms are affixed to nodes (2,4), (4,4), (4,0), (2,0), (7,4), (10,2) and (7,0). Nodes (5,2) and (6,2) are connected by a single bond.

The carbon atoms present are connected by either a single or double bonds, taking into consideration the principle of resonance and/or tautomerism.

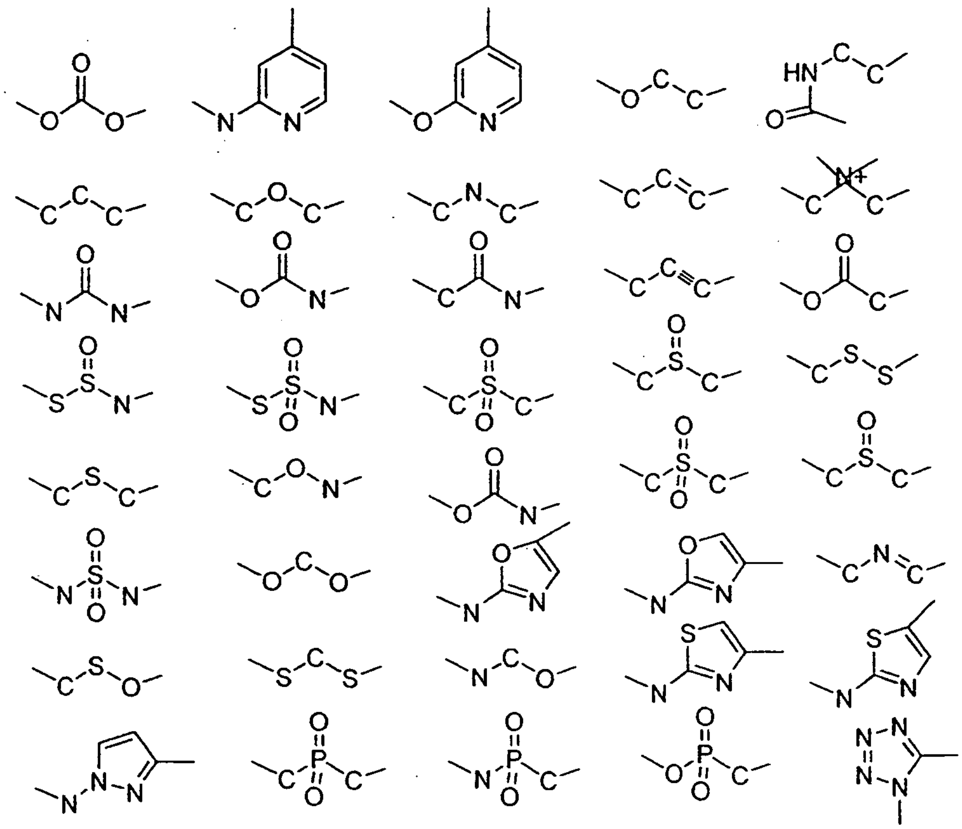
The intersection of the framework (linker) and the ligand group, and indeed, the framework (linker) itself can have many different bonding patterns. Examples of acceptable patterns of three contiguous atom arrangements are shown in the following diagram:

C C C	N C C	O C C	S C C	P C C
C C N	N C N	O C N	S C N	P C N
C C O	N C O	O C O	S C O	P C O
C C S	N C S	O C S	S C S	P C S
C C P	N C P	O C P	S C P	P C P
C N C	N N C	O N C	S N C	P N C
C N N	N N N	O N N	S N N	P N N
C N O	N N O	O N O	S N O	P N O
C N S	N N S	O N S	S N S	P N S
C N P	N N P	O N P	S N P	P N P
C O C	N O C	O O C	S O C	P O C
C O O	N O N	O O N	S O N	P O N
C O C	N O O	O O O	S O O	P O O
C O P	N O P	O O S	S O S	P O S
		O O P	S O P	P O P
C S C	N S C	O S C	S S C	P S C
C S N	N S N	O S N	S S N	P S N
C S O	N S O	O S O	S S O	P S O
C S S	N S S	O S S	S S S	P S S
C S P	N S P	O S P	S S P	P S P
C P C	N P C	O P C	S P C	P P C
C P N	N P N	O P N	S P N	P P N
C P O	N P O	O P O	S P O	P P O
C P S	N P S	O P S	S P S	P P S
C P P	N P P	O P P	S P P	P P P

One skilled in the art would be able to identify bonding patterns that would produce multivalent compounds. Methods for producing these bonding arrangements are described in March, "Advanced Organic Chemistry", 4th Edition, Wiley-Interscience, New York, New York (1992). These arrangements are described in the grid of dots shown in the scheme above. All of the possible arrangements for the five most preferred atoms are shown. Each atom has a variety

of acceptable oxidation states. The bonding arrangements underlined are less acceptable and are not preferred.

Examples of molecular structures in which the above bonding patterns could be employed as components of the linker are shown below.



The identification of an appropriate framework geometry and size for ligand domain presentation are important steps in the construction of a multibinding compound with enhanced activity. Systematic spatial searching strategies can be used to aid in the identification of preferred frameworks through an iterative process. Figure 4 illustrates a useful strategy for determining an optimal framework display orientation for ligand domains. Various other strategies are known to those skilled in the art of molecular design and can be used for preparing compounds of this invention.

As shown in Figure 3, display vectors around similar central core structures such as a phenyl structure (Panel A) and a cyclohexane structure (Panel B) can be varied, as can the spacing of the ligand domain from the core structure (i.e., the length of the attaching moiety). It is to be noted that core structures other than those shown here can be used for determining the optimal framework display orientation of the ligands. The process may require the use of multiple copies of the same central core structure or combinations of different types of display cores.

The above-described process can be extended to trimers (Figure 3) and compound of higher valency. (Figure 4)

Assays of each of the individual compounds of a collection generated as described above will lead to a subset of compounds with the desired enhanced activities (e.g., potency, selectivity, etc.). The analysis of this subset using a technique such as Ensemble Molecular Dynamics will provide a framework orientation that favors the properties desired. A wide diversity of linkers is commercially available (see, e.g., Available Chemical Directory (ACD)). Many of the linkers that are suitable for use in this invention fall into this category. Other can be readily synthesized by methods well known in the art and/or are described below.

Having selected a preferred framework geometry, the physical properties of the linker can be optimized by varying the chemical composition thereof. The composition of the linker can be varied in numerous ways to achieve the desired physical properties for the multibinding compound.

It can therefore be seen that there is a plethora of possibilities for the composition of a linker. Examples of linkers include aliphatic moieties, aromatic moieties, steroidal moieties, peptides, and the like. Specific examples are peptides or polyamides, hydrocarbons, aromatic groups, ethers, lipids, cationic or anionic groups, or a combination thereof.

Examples are given below, but it should be understood that various changes may be made and equivalents may be substituted without departing from the true spirit and scope of the invention. For example, properties of the linker can be

modified by the addition or insertion of ancillary groups into or onto the linker, for example, to change the solubility of the multibinding compound (in water, fats, lipids, biological fluids, etc.), hydrophobicity, hydrophilicity, linker flexibility, antigenicity, stability, and the like. For example, the introduction of one or more poly(ethylene glycol) (PEG) groups onto or into the linker enhances the hydrophilicity and water solubility of the multibinding compound, increases both molecular weight and molecular size and, depending on the nature of the unPEGylated linker, may increase the *in vivo* retention time. Further PEG may decrease antigenicity and potentially enhances the overall rigidity of the linker.

Ancillary groups which enhance the water solubility/hydrophilicity of the linker and, accordingly, the resulting multibinding compounds are useful in practicing this invention. Thus, it is within the scope of the present invention to use ancillary groups such as, for example, small repeating units of ethylene glycols, alcohols, polyols (e.g., glycerin, glycerol propoxylate, saccharides, including mono-, oligosaccharides, etc.), carboxylates (e.g., small repeating units of glutamic acid, acrylic acid, etc.), amines (e.g., tetraethylenepentamine), and the like) to enhance the water solubility and/or hydrophilicity of the multibinding compounds of this invention. In preferred embodiments, the ancillary group used to improve water solubility/hydrophilicity will be a polyether .

The incorporation of lipophilic ancillary groups within the structure of the linker to enhance the lipophilicity and/or hydrophobicity of the multibinding compounds described herein is also within the scope of this invention. Lipophilic groups useful with the linkers of this invention include, by way of example only, aryl and heteroaryl groups which, as above, may be either unsubstituted or substituted with other groups, but are at least substituted with a group which allows their covalent attachment to the linker. Other lipophilic groups useful with the linkers of this invention include fatty acid derivatives which do not form bilayers in aqueous medium until higher concentrations are reached.

Also within the scope of this invention is the use of ancillary groups which result in the multibinding compound being incorporated or anchored into a vesicle

or other membranous structure such as a liposome or a micelle. The term "lipid" refers to any fatty acid derivative that is capable of forming a bilayer or a micelle such that a hydrophobic portion of the lipid material orients toward the bilayer while a hydrophilic portion orients toward the aqueous phase. Hydrophilic characteristics derive from the presence of phosphato, carboxylic, sulfato, amino, sulfhydryl, nitro and other like groups well known in the art. Hydrophobicity could be conferred by the inclusion of groups that include, but are not limited to, long chain saturated and unsaturated aliphatic hydrocarbon groups of up to 20 carbon atoms and such groups substituted by one or more aryl, heteroaryl, cycloalkyl, and/or heterocyclic group(s). Preferred lipids are phosphglycerides and sphingolipids, representative examples of which include phosphatidylcholine, phosphatidylethanolamine, phosphatidylserine, phosphatidylinositol, phosphatidic acid, palmitoyleoyl phosphatidylcholine, lysophosphatidylcholine, lysophosphatidyl-ethanolamine, dipalmitoylphosphatidylcholine, dioleoylphosphatidylcholine, distearoyl-phosphatidylcholine or dilinoleoylphosphatidylcholine could be used. Other compounds lacking phosphorus, such as sphingolipid and glycosphingolipid families are also within the group designated as lipid. Additionally, the amphipathic lipids described above may be mixed with other lipids including triglycerides and sterols.

The flexibility of the linker can be manipulated by the inclusion of ancillary groups which are bulky and/or rigid. The presence of bulky or rigid groups can hinder free rotation about bonds in the linker or bonds between the linker and the ancillary group(s) or bonds between the linker and the functional groups. Rigid groups can include, for example, those groups whose conformational lability is restrained by the presence of rings and/or multiple bonds within the group, for example, aryl, heteroaryl, cycloalkyl, cycloalkenyl, and heterocyclic groups. Other groups which can impart rigidity include polypeptide groups such as oligo- or polyproline chains.

Rigidity can also be imparted electrostatically. Thus, if the ancillary groups are either positively or negatively charged, the similarly charged ancillary groups

will force the presenter linker into a configuration affording the maximum distance between each of the like charges. The energetic cost of bringing the like-charged groups closer to each other will tend to hold the linker in a configuration that maintains the separation between the like-charged ancillary groups. Further ancillary groups bearing opposite charges will tend to be attracted to their oppositely charged counterparts and potentially may enter into both inter- and intramolecular ionic bonds. This non-covalent mechanism will tend to hold the linker into a conformation which allows bonding between the oppositely charged groups. The addition of ancillary groups which are charged, or alternatively, bear a latent charge when deprotected, following addition to the linker, include deprotectation of a carboxyl, hydroxyl, thiol or amino group by a change in pH, oxidation, reduction or other mechanisms known to those skilled in the art which result in removal of the protecting group, is within the scope of this invention.

Rigidity may also be imparted by internal hydrogen bonding or by hydrophobic collapse.

Bulky groups can include, for example, large atoms, ions (e.g., iodine, sulfur, metal ions, etc.) or groups containing large atoms, polycyclic groups, including aromatic groups, non-aromatic groups and structures incorporating one or more carbon-carbon multiple bonds (i.e., alkenes and alkynes). Bulky groups can also include oligomers and polymers which are branched- or straight-chain species. Species that are branched are expected to increase the rigidity of the structure more per unit molecular weight gain than are straight-chain species.

In preferred embodiments, rigidity is imparted by the presence of cyclic groups (e.g., aryl, heteroaryl, cycloalkyl, heterocyclic, etc.). In other preferred embodiments, the linker comprises one or more six-membered rings. In still further preferred embodiments, the ring is an aryl group such as, for example, phenyl or naphthyl.

In view of the above, it is apparent that the appropriate selection of a linker group providing suitable orientation, restricted/unrestricted rotation, the desired degree of hydrophobicity/hydrophilicity, etc. is well within the skill of the art.

Eliminating or reducing antigenicity of the multibinding compounds described herein is also within the scope of this invention. In certain cases, the antigenicity of a multibinding compound may be eliminated or reduced by use of groups such as, for example, poly(ethylene glycol).

As explained above, the multibinding compounds described herein comprise 2-10 ligands attached to a linker that attaches the ligands in such a manner that they are presented to the enzyme for multivalent interactions with ligand binding sites thereon/therein. The linker spatially constrains these interactions to occur within dimensions defined by the linker. This and other factors increases the biological activity of the multibinding compound as compared to the same number of ligands made available in monobinding form.

The compounds of this invention are preferably represented by the empirical Formula $(L)_p(X)_q$ where L, X, p and q are as defined above. This is intended to include the several ways in which the ligands can be linked together in order to achieve the objective of multivalency, and a more detailed explanation is described below.

As noted previously, the linker may be considered as a framework to which ligands are attached. Thus, it should be recognized that the ligands can be attached at any suitable position on this framework, for example, at the termini of a linear chain or at any intermediate position.

The simplest and most preferred multibinding compound is a bivalent compound which can be represented as L-X-L, where each L is independently a ligand which may be the same or different and each X is independently the linker. Examples of such bivalent compounds are provided in FIG. 1 where each shaded circle represents a ligand. A trivalent compound could also be represented in a linear fashion, i.e., as a sequence of repeated units L-X-L-X-L, in which L is a ligand and is the same or different at each occurrence, as can X. However, a trimer can also be a radial multibinding compound comprising three ligands attached to a central core, and thus represented as $(L)_3X$, where the linker X could include, for example, an aryl or cycloalkyl group. Illustrations of trivalent and tetravalent

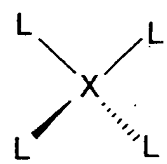
compounds of this invention are found in FIGs 2 and 3 respectively where, again, the shaded circles represent ligands. Tetravalent compounds can be represented in a linear array, e.g.,

L-X-L-X-L-X-L

in a branched array, e.g.,

```
L-X-L-X-L
    |
    L
```

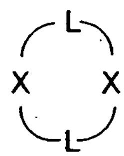
(a branched construct analogous to the isomers of butane -- *n*-butyl, *iso*-butyl, *sec*-butyl, and *t*-butyl) or in a tetrahedral array, e.g.,



where X and L are as defined herein. Alternatively, it could be represented as an alkyl, aryl or cycloalkyl derivative as above with four (4) ligands attached to the core linker.

The same considerations apply to higher multibinding compounds of this invention containing 5-10 ligands as illustrated in FIG. 4 where, as before, the shaded circles represent ligands. However, for multibinding agents attached to a central linker such as aryl or cycloalkyl, there is a self-evident constraint that there must be sufficient attachment sites on the linker to accommodate the number of ligands present; for example, a benzene ring could not directly accommodate more than 6 ligands, whereas a multi-ring linker (e.g., biphenyl) could accommodate a larger number of ligands.

The above described compounds may alternatively be represented as cyclic chains of the form:



and variants thereof.

All of the above variations are intended to be within the scope of the invention defined by the Formula $(L)_p(X)_q$.

With the foregoing in mind, a preferred linker may be represented by the following formula:

$$-X^a-Z-(Y^a-Z)_m-Y^b-Z-X^a-$$

in which:

m is an integer of from 0 to 20;

X^a at each separate occurrence is selected from the group consisting of -O-, -S-, -NR-, -C(O)-, -C(O)O-, -C(O)NR-, -C(S), -C(S)O-, -C(S)NR- or a covalent bond where R is as defined below;

Z is at each separate occurrence is selected from the group consisting of alkylene, substituted alkylene, cycloalkylene, substituted cylcoalkylene, alkenylene, substituted alkenylene, alkynylene, substituted alkynylene, cycloalkenylene, substituted cycloalkenylene, arylene, heteroarylene, heterocyclene, or a covalent bond;

Y^a and Y^b at each separate occurrence are selected from the group consisting of -O-, -C(O)-, -OC(O)-, -C(O)O-, -NR-, -S(O)n-, -C(O)NR'-, -NR' C(O)-, -NR' C(O)NR'-, -NR' C(S)NR'-, -C(=NR')-NR'-, -NR'-C(=NR')-, -OC(O)-NR'-, -NR'-C(O)-O-, -N=C(X^a)-NR'-, -NR'-C(X^a)=N-,-P(O)(OR')-O-, -O-P(O)(OR')-, -$S(O)_n$CR' R"-, -$S(O)_n$-NR'-, -NR'-$S(O)_n$-, -S-S-, and a covalent bond; where n is 0, 1 or 2; and R, R' and R" at each separate occurrence are selected from the group

consisting of hydrogen, alkyl, substituted alkyl, cycloalkyl, substituted cycloalkyl, alkenyl, substituted alkenyl, cycloalkenyl, substituted cycloalkenyl, alkynyl, substituted alkynyl, aryl, heteroaryl and heterocyclic.

Additionally, the linker moiety can be optionally substituted at any atom therein by one or more alkyl, substituted alkyl, cycloalkyl, substituted cycloalkyl, alkenyl, substituted alkenyl, cycloalkenyl, substituted cycloalkenyl, alkynyl, substituted alkynyl, aryl, heteroaryl and heterocyclic group.

In one embodiment of this invention, the linker (i.e., X, X' or X") is selected those shown in Table II:

Table II

Representative Linkers

Linker
$-(CH_2)_n-$ where n is an integer of from 2-10
$-(CH_2)_2-O-(CH_2)_2-O-(CH_2)_2-$
$-CH_2-Z-CH_2-$ where Z is 1,4-phenylene
$-(CHCO_2Et)-(CH_2)_2-(CHCO_2Et)-$
$-CH_2-Z-CH_2-$ where Z is 2,3-quinoxaline
$-(CH_2)-(CH{=}CH)-(CH_2)-$
$-(CH_2)-C(O)-C(O)-(CH_2)-$
$-(CH_2)-(C{\equiv}C)-(CH_2)-$
$-CH_2-Z-CH_2-$ where Z is 1,2-phenylene
$-(CH_2)-C(O)-(CH_2)-$
$-(CH_2)-CH(COOH)-(CH_2)-$
$-(CH_2)-CH(COOEt)-(CH_2)-$
$-(CH_2)-CH(OH)-(CH_2)-$
$-CH(CH_3)-(CH_2)-$
$-CH(CN)-(CH_2)-$

Linker
$-CH_2-Z-CH_2-$ where Z is 2,6-pyridyl
$-(CH_2)-C(=CH_2)-(CH_2)-$
$-(CH_2)-CH(OH)-CH(OH)-(CH_2)-$
$-(CH_2)_2-N(CH_3)-(CH_2)_2-$
$-(CH_2)_2-O-(CH_2)_2-$
$-(CH_2)-Z-(CH_2)-$ where Z is 4-biphenyl
$-CH_2-Z-CH_2-$ where Z is 1,2-phenylene
$-CH_2-Z-CH_2-$ where Z is 1,3-phenylene
$-CH_2-O-C(O)-NH-Z-NH-C(O)-O-CH_2-$ where Z is 1,3-phenylene
$-CH_2-O-C(O)-(CH_2)_8-C(O)-O-CH_2-$
$-CH_2-O-C(O)-(CH_2)_{10}-C(O)-O-CH_2-$
$-CH_2-O-C(O)-Z-C(O)-O-CH_2-$ where Z is 1,3-phenylene
$-CH_2-O-C(O)-(CH_2)_6-C(O)-O-CH_2-$
$-CH_2-O-C(O)-Z-C(O)-O-CH_2-$ where Z is 1,4-phenylene
$-CH_2-O-C(O)-Z-C(O)-O-CH_2-$ where Z is 2,3-(5-norbornene)

In view of the above description of the linker, it is understood that the term "linker" when used in combination with the term "multibinding compound" includes both a covalently contiguous single linker (e.g., L-X-L) and multiple covalently non-contiguous linkers (L-X-L-X-L) within the multibinding compound.

Combinatorial Libraries

The methods described above lend themselves to combinatorial approaches for identifying multimeric compounds which possess multibinding properties.

Specifically, factors such as the proper juxtaposition of the individual ligands of a multibinding compound with respect to the relevant array of binding sites on a target or targets is important in optimizing the interaction of the

multibinding compound with its target(s) and to maximize the biological advantage through multivalency. One approach is to identify a library of candidate multibinding compounds with properties spanning the multibinding parameters that are relevant for a particular target. These parameters include: (1) the identity of ligand(s), (2) the orientation of ligands, (3) the valency of the construct, (4) linker length, (5) linker geometry, (6) linker physical properties, and (7) linker chemical functional groups.

Libraries of multimeric compounds potentially possessing multibinding properties (i.e., candidate multibinding compounds) and comprising a multiplicity of such variables are prepared and these libraries are then evaluated via conventional assays corresponding to the ligand selected and the multibinding parameters desired. Considerations relevant to each of these variables are set forth below:

Selection of ligand(s):

A single ligand or set of ligands is (are) selected for incorporation into the libraries of candidate multibinding compounds which library is directed against a particular biological target or targets, i.e., antagonism of a muscarinic receptor. The only requirement for the ligands chosen is that they are capable of interacting with the selected target(s). Thus, ligands may be known drugs, modified forms of known drugs, substructures of known drugs or substrates of modified forms of known drugs (which are competent to interact with the target), or other compounds. Ligands are preferably chosen based on known favorable properties that may be projected to be carried over to or amplified in multibinding forms. Favorable properties include demonstrated safety and efficacy in human patients, appropriate PK/ADME profiles, synthetic accessibility, and desirable physical properties such as solubility, log P, etc. However, it is crucial to note that ligands which display an unfavorable property from among the previous list may obtain a more favorable property through the process of multibinding compound formation; i.e., ligands should not necessarily be excluded on such a basis. For example, a ligand that is not sufficiently potent at a particular target so as to be efficacious in a human

patient may become highly potent and efficacious when presented in multibinding form. A ligand that is potent and efficacious but not of utility because of a non-mechanism-related toxic side effect may have increased therapeutic index (increased potency relative to toxicity) as a multibinding compound. Compounds that exhibit short *in vivo* half-lives may have extended half-lives as multibinding compounds. Physical properties of ligands that limit their usefulness (e.g. poor bioavailability due to low solubility, hydrophobicity, hydrophilicity) may be rationally modulated in multibinding forms, providing compounds with physical properties consistent with the desired utility.

<u>Orientation: selection of ligand attachment points and linking chemistry</u>

Several points are chosen on each ligand at which to attach the ligand to the linker. The selected points on the ligand/linker for attachment are functionalized to contain complementary reactive functional groups. This permits probing the effects of presenting the ligands to their receptor(s) in multiple relative orientations, an important multibinding design parameter. The only requirement for choosing attachment points is that attaching to at least one of these points does not abrogate activity of the ligand. Such points for attachment can be identified by structural information when available. For example, inspection of a co-crystal structure of a protease inhibitor bound to its target allows one to identify one or more sites where linker attachment will not preclude the enzyme:inhibitor interaction. Alternatively, evaluation of ligand/target binding by nuclear magnetic resonance will permit the identification of sites non-essential for ligand/target binding. See, for example, Fesik, et al., U.S. Patent No. 5,891,643. When such structural information is not available, utilization of structure-activity relationships (SAR) for ligands will suggest positions where substantial structural variations are and are not allowed. In the absence of both structural and SAR information, a library is merely selected with multiple points of attachment to allow presentation of the ligand in multiple distinct orientations. Subsequent evaluation of this library will indicate what positions are suitable for attachment.

It is important to emphasize that positions of attachment that do abrogate the activity of the monomeric ligand may also be advantageously included in candidate multibinding compounds in the library provided that such compounds bear at least one ligand attached in a manner which does not abrogate intrinsic activity. This selection derives from, for example, heterobivalent interactions within the context of a single target molecule. For example, consider a receptor antagonist ligand bound to its target receptor, and then consider modifying this ligand by attaching to it a second copy of the same ligand with a linker which allows the second ligand to interact with the same receptor molecule at sites proximal to the antagonist binding site, which include elements of the receptor that are not part of the formal antagonist binding site and/or elements of the matrix surrounding the receptor such as the membrane. Here, the most favorable orientation for interaction of the second ligand molecule with the receptor/matrix may be achieved by attaching it to the linker at a position which abrogates activity of the ligand at the formal antagonist binding site. Another way to consider this is that the SAR of individual ligands within the context of a multibinding structure is often different from the SAR of those same ligands in momomeric form.

The foregoing discussion focused on bivalent interactions of dimeric compounds bearing two copies of the same ligand joined to a single linker through different attachment points, one of which may abrogate the binding/activity of the monomeric ligand. It should also be understood that bivalent advantage may also be attained with heterodimeric constructs bearing two different ligands that bind to common or different targets. For example, a $5HT_4$ receptor antagonist and a bladder-selective muscarinic M_3 antagonist may be joined to a linker through attachment points which do not abrogate the binding affinity of the monomeric ligands for their respective receptor sites. The dimeric compound may achieve enhanced affinity for both receptors due to favorable interactions between the $5HT_4$ ligand and elements of the M_3 receptor proximal to the formal M_3 antagonist binding site and between the M_3 ligand and elements of the $5HT_4$ receptor proximal to the formal $5HT_4$ antagonist binding site. Thus, the dimeric compound may be

more potent and selective antagonist of overactive bladder and a superior therapy for urinary urge incontinence.

Once the ligand attachment points have been chosen, one identifies the types of chemical linkages that are possible at those points. The most preferred types of chemical linkages are those that are compatible with the overall structure of the ligand (or protected forms of the ligand) readily and generally formed, stable and intrinsically inocuous under typical chemical and physiological conditions, and compatible with a large number of available linkers. Amide bonds, ethers, amines, carbamates, ureas, and sulfonamides are but a few examples of preferred linkages.

Linkers: spanning relevant multibinding parameters through selection of valency, linker length, linker geometry, rigidity, physical properties, and chemical functional groups

In the library of linkers employed to generate the library of candidate multibinding compounds, the selection of linkers employed in this library of linkers takes into consideration the following factors:

Valency:

In most instances the library of linkers is initiated with divalent linkers. The choice of ligands and proper juxtaposition of two ligands relative to their binding sites permits such molecules to exhibit target binding affinities and specificities more than sufficient to confer biological advantage. Furthermore, divalent linkers or constructs are also typically of modest size such that they retain the desirable biodistribution properties of small molecules.

Linker length:

Linkers are chosen in a range of lengths to allow the spanning of a range of inter-ligand distances that encompass the distance preferable for a given divalent interaction. In some instances the preferred distance can be estimated rather precisely from high-resolution structural information of targets, typically enzymes and soluble receptor targets. In other instances where high-resolution structural information is not available (such as 7TM G-protein coupled receptors), one can make use of simple models to estimate the maximum distance between binding sites

either on adjacent receptors or at different locations on the same receptor. In situations where two binding sites are present on the same target (or target subunit for multisubunit targets), preferred linker distances are 2-20 Å, with more preferred linker distances of 3-12 Å. In situations where two binding sites reside on separate (e.g., protein) target sites, preferred linker distances are 20-100 Å, with more preferred distances of 30-70 Å.

Linker geometry and rigidity:

The combination of ligand attachment site, linker length, linker geometry, and linker rigidity determine the possible ways in which the ligands of candidate multibinding compounds may be displayed in three dimensions and thereby presented to their binding sites. Linker geometry and rigidity are nominally determined by chemical composition and bonding pattern, which may be controlled and are systematically varied as another spanning function in a multibinding array. For example, linker geometry is varied by attaching two ligands to the ortho, meta, and para positions of a benzene ring, or in *cis*- or *trans*-arrangements at the 1,1- vs. 1,2- vs. 1,3- vs. 1,4- positions around a cyclohexane core or in *cis*- or *trans*-arrangements at a point of ethylene unsaturation. Linker rigidity is varied by controlling the number and relative energies of different conformational states possible for the linker. For example, a divalent compound bearing two ligands joined by 1,8-octyl linker has many more degrees of freedom, and is therefore less rigid than a compound in which the two ligands are attached to the 4,4' positions of a biphenyl linker.

Linker physical properties:

The physical properties of linkers are nominally determined by the chemical constitution and bonding patterns of the linker, and linker physical properties impact the overall physical properties of the candidate multibinding compounds in which they are included. A range of linker compositions is typically selected to provide a range of physical properties (hydrophobicity, hydrophilicity, amphiphilicity, polarization, acidity, and basicity) in the candidate multibinding compounds. The particular choice of linker physical properties is made within the

context of the physical properties of the ligands they join and preferably the goal is to generate molecules with favorable PK/ADME properties. For example, linkers can be selected to avoid those that are too hydrophilic or too hydrophobic to be readily absorbed and/or distributed *in vivo*.

Linker chemical functional groups:

Linker chemical functional groups are selected to be compatible with the chemistry chosen to connect linkers to the ligands and to impart the range of physical properties sufficient to span initial examination of this parameter.

Combinatorial synthesis:

Having chosen a set of *n* ligands (*n* being determined by the sum of the number of different attachment points for each ligand chosen) and *m* linkers by the process outlined above, a library of $(n!)m$ candidate divalent multibinding compounds is prepared which spans the relevant multibinding design parameters for a particular target. For example, an array generated from two ligands, one which has two attachment points (A1, A2) and one which has three attachment points (B1, B2, B3) joined in all possible combinations provide for at least 15 possible combinations of multibinding compounds:

A1-A1	A1-A2	A1-B1	A1-B2	A1-B3	A2-A2	A2-B1	A2-B2
A2-B3	B1-B1	B1-B2	B1-B3	B2-B2	B2-B3	B3-B3	

When each of these combinations is joined by 10 different linkers, a library of 150 candidate multibinding compounds results.

Given the combinatorial nature of the library, common chemistries are preferably used to join the reactive functionalies on the ligands with complementary reactive functionalities on the linkers. The library therefore lends itself to efficient parallel synthetic methods. The combinatorial library can employ solid phase chemistries well known in the art wherein the ligand and/or linker is attached to a solid support. Alternatively and preferably, the combinatorial libary is prepared in

the solution phase. After synthesis, candidate multibinding compounds are optionally purified before assaying for activity by, for example, chromatographic methods (e.g., HPLC).

Analysis of array by biochemical, analytical, pharmacological, and computational methods:

Various methods are used to characterize the properties and activities of the candidate multibinding compounds in the library to determine which compounds possess multibinding properties. Physical constants such as solubility under various solvent conditions and logD/clogD values can be determined. A combination of NMR spectroscopy and computational methods is used to determine low-energy conformations of the candidate multibinding compounds in fluid media. The ability of the members of the library to bind to the desired target and other targets is determined by various standard methods, which include radioligand displacement assays for receptor and ion channel targets, and kinetic inhibition analysis for many enzyme targets. *In vitro* efficacy, such as for receptor agonists and antagonists, ion channel blockers, and antimicrobial activity, can also be determined. Pharmacological data, including oral absorption, everted gut penetration, other pharmacokinetic parameters and efficacy data can be determined in appropriate models. In this way, key structure-activity relationships are obtained for multibinding design parameters which are then used to direct future work.

The members of the library which exhibit multibinding properties, as defined herein, can be readily determined by conventional methods. First those members which exhibit multibinding properties are identified by conventional methods as described above including conventional assays (both *in vitro* and *in vivo*).

Second, ascertaining the structure of those compounds which exhibit multibinding properties can be accomplished via art recognized procedures. For example, each member of the library can be encrypted or tagged with appropriate information allowing determination of the structure of relevant members at a later time. See, for example, Dower, et al., International Patent Application Publication

No. WO 93/06121; Brenner, et al., Proc. Natl. Acad. Sci., USA, 89:5181 (1992); Gallop, et al., U.S. Patent No. 5,846,839; each of which are incorporated herein by reference in its entirety. Alternatively, the structure of relevant multivalent compounds can also be determined from soluble and untagged libaries of candidate multivalent compounds by methods known in the art such as those described by Hindsgaul, et al., Canadian Patent Application No. 2,240,325 which was published on July 11, 1998. Such methods couple frontal affinity chromatography with mass spectroscopy to determine both the structure and relative binding affinities of candidate multibinding compounds to receptors.

The process set forth above for dimeric candidate multibinding compounds can, of course, be extended to trimeric candidate compounds and higher analogs thereof.

Follow-up synthesis and analysis of additional array(s):

Based on the information obtained through analysis of the initial library, an optional component of the process is to ascertain one or more promising multibinding "lead" compounds as defined by particular relative ligand orientations, linker lengths, linker geometries, etc. Additional libraries can then be generated around these leads to provide for further information regarding structure to activity relationships. These arrays typically bear more focused variations in linker structure in an effort to further optimize target affinity and/or activity at the target (antagonism, partial agonism, etc.), and/or alter physical properties. By iterative redesign/analysis using the novel principles of multibinding design along with classical medicinal chemistry, biochemistry, and pharmacology approaches, one is able to prepare and identify optimal multibinding compounds that exhibit biological advantage towards their targets and as therapeutic agents.

To further elaborate upon this procedure, suitable divalent linkers include, by way of example only, those derived from dicarboxylic acids, disulfonylhalides, dialdehydes, diketones, dihalides, diisocyanates,diamines, diols, mixtures of carboxylic acids, sulfonylhalides, aldehydes, ketones, halides, isocyanates, amines and diols. In each case, the carboxylic acid, sulfonylhalide, aldehyde, ketone,

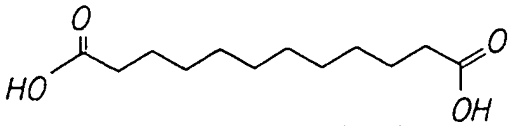
halide, isocyanate, amine and diol functional group is reacted with a complementary functionality on the ligand to form a covalent linkage. Such complementary functionality is well known in the art as illustrated in the following table:

COMPLEMENTARY BINDING CHEMISTRIES

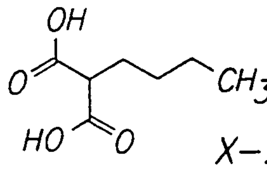
First Reactive Group	Second Reactive Group	Linkage
hydroxyl	isocyanate	urethane
amine	epoxide	β-amine
hydroxyamine	sulfonyl halide	sulfonamide
carboxyl acid	amine	amide
hydroxyl	alkyl/aryl halide	ether
aldehyde	amine/$NaCNBH_3$	amine
ketone	amine/$NaCNBH_3$	amine
amine	isocyanate	urea

Exemplary linkers include the following linkers identified as X-1 through X-418 as set forth below:

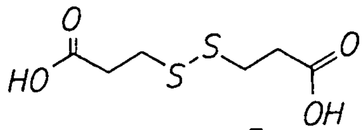
Diacids



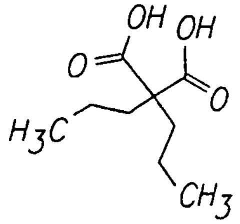
X-1



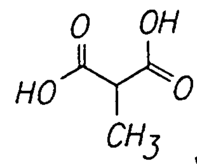
X-2



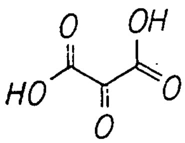
X-3



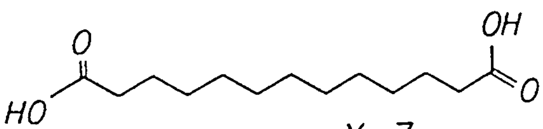
X-4



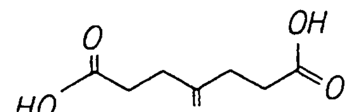
X-5



X-6



X-7



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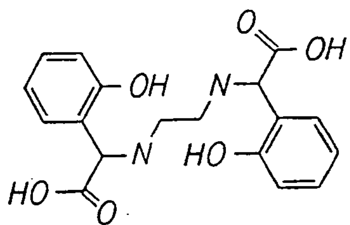

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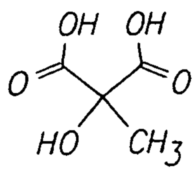

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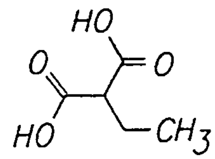

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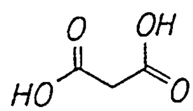

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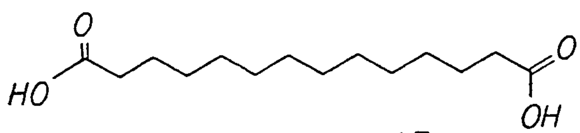

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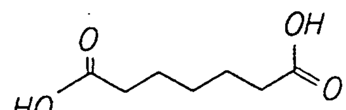

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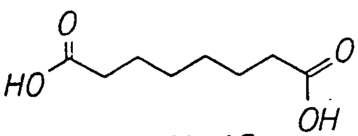

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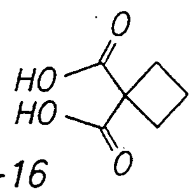

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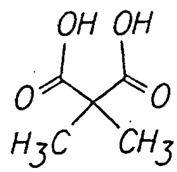

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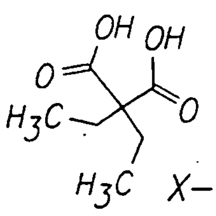

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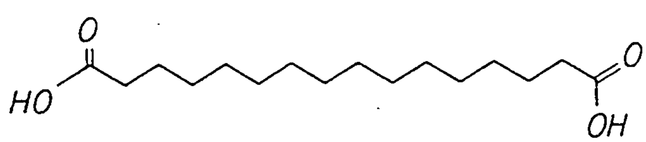

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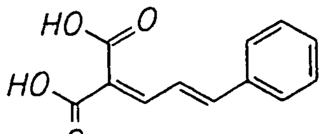

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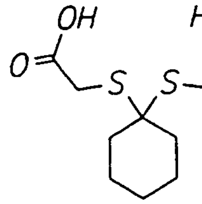

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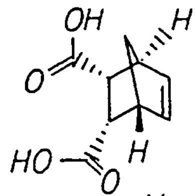

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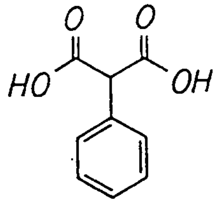

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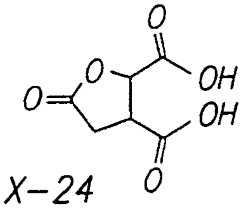

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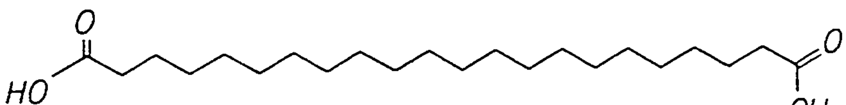

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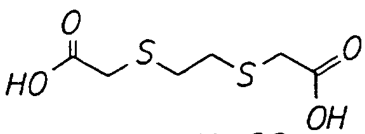

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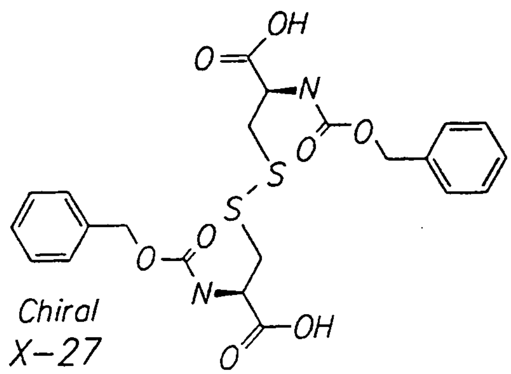

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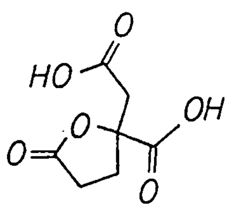

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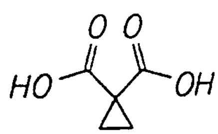

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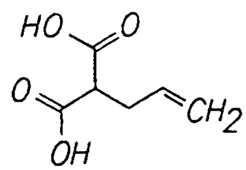

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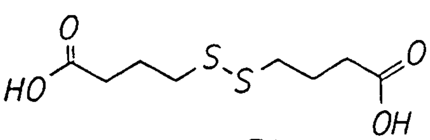

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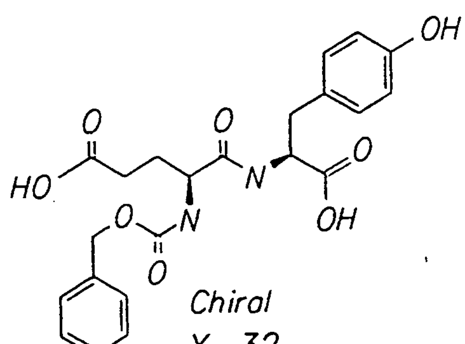

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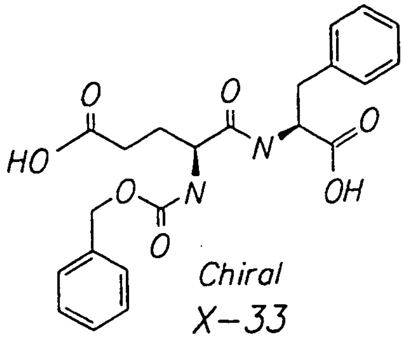

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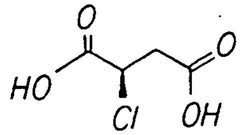

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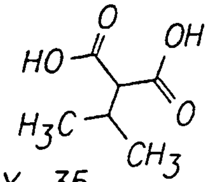

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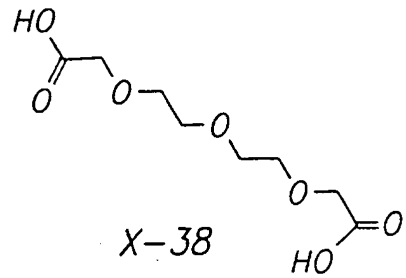

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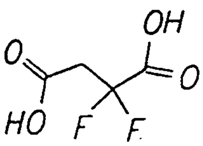

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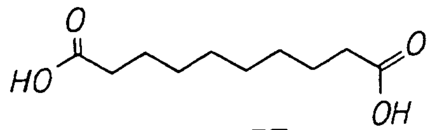

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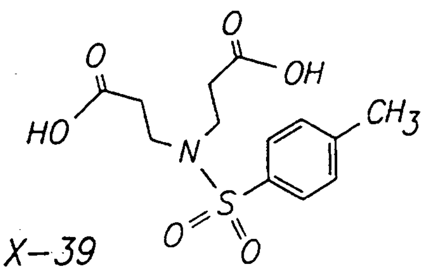

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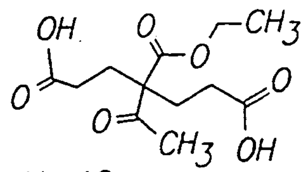

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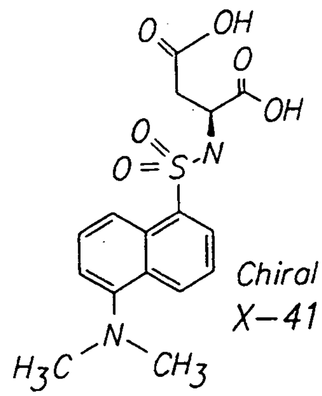

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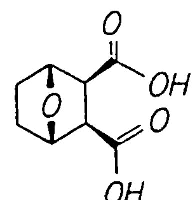

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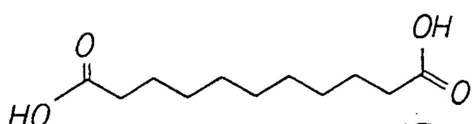

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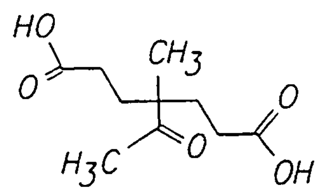

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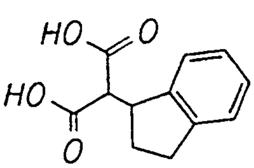

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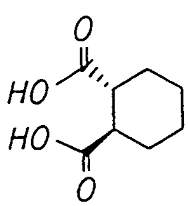

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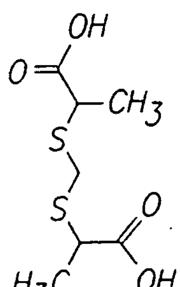

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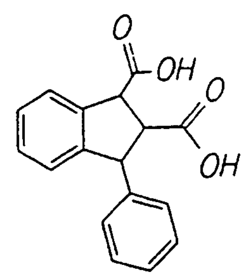

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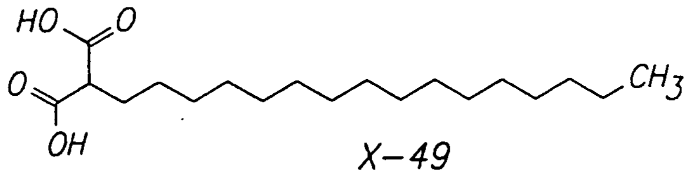
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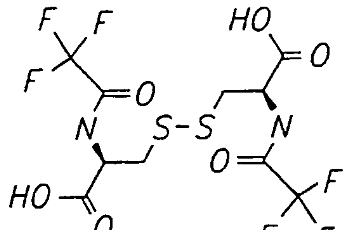
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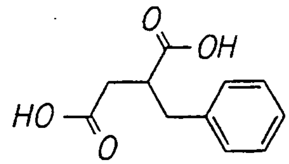
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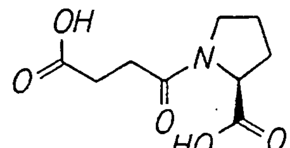
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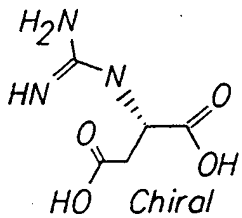
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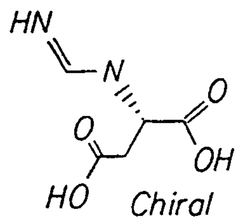
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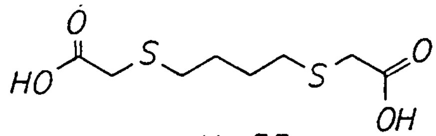
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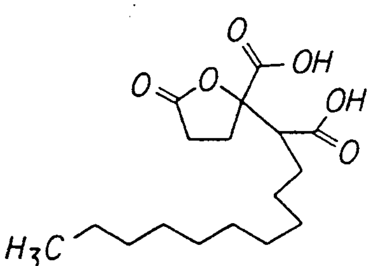
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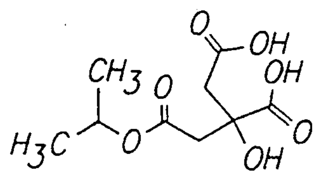
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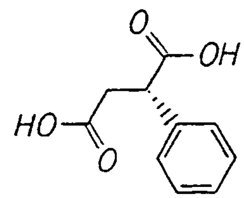
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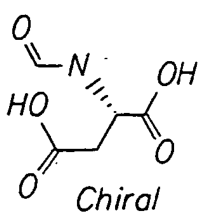
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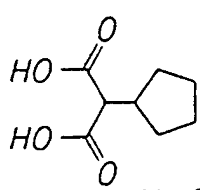
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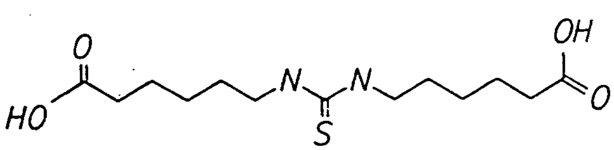
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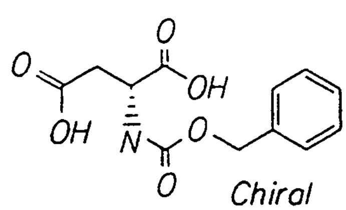
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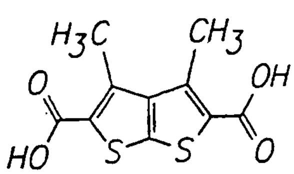

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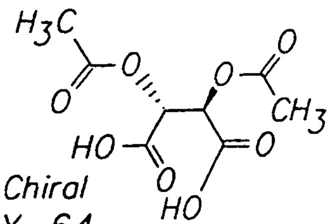

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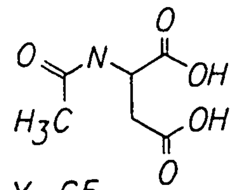

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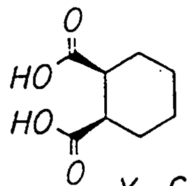

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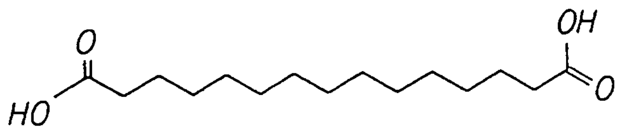

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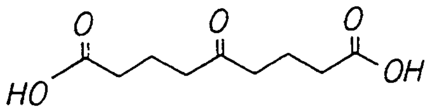

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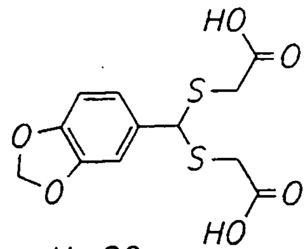

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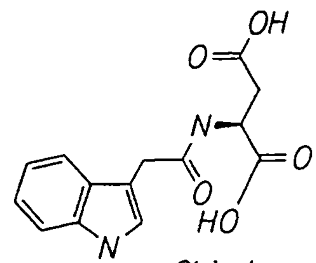

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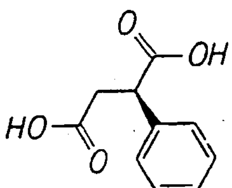

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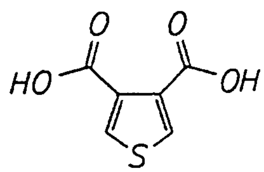

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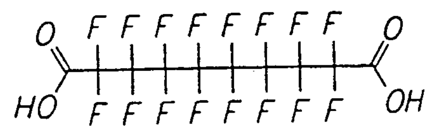

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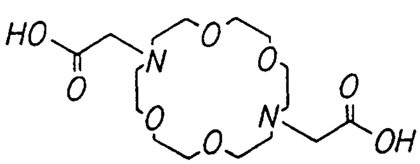

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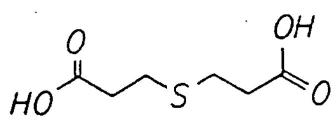

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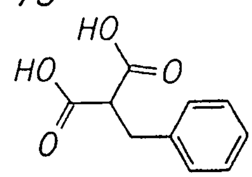

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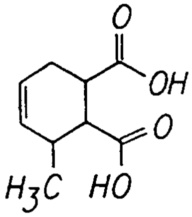

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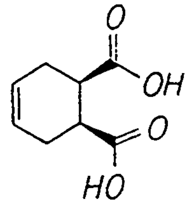

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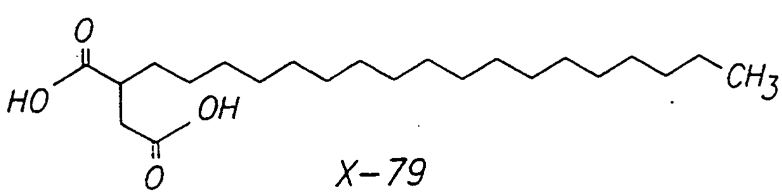

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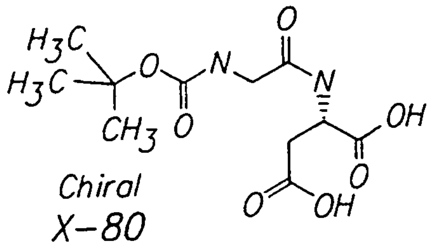

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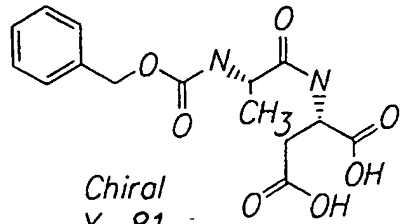

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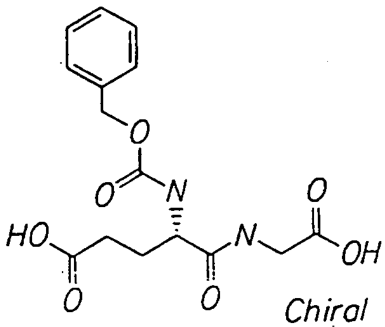

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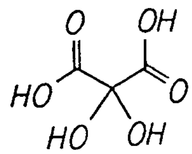

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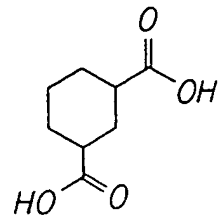

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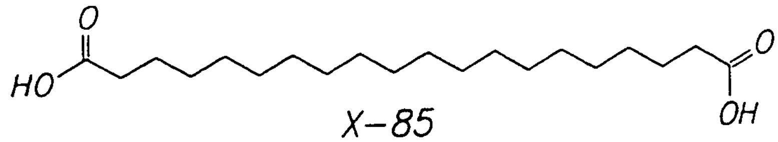
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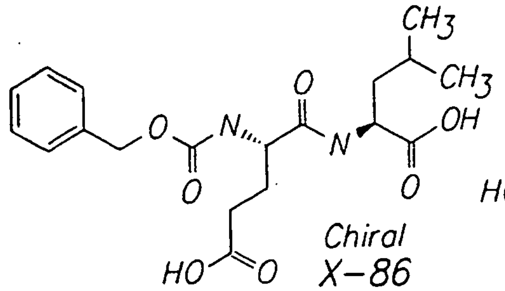
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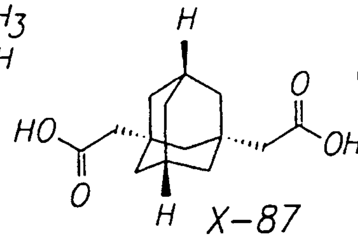
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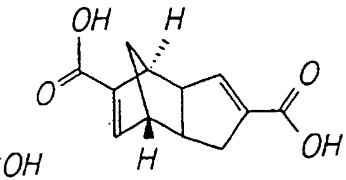
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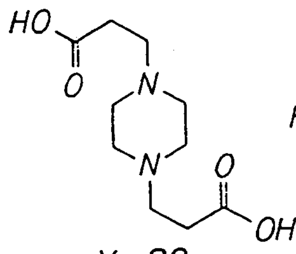
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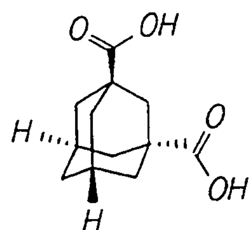
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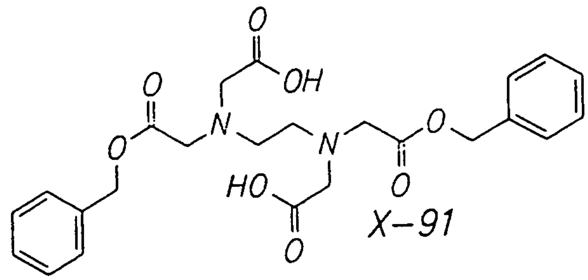
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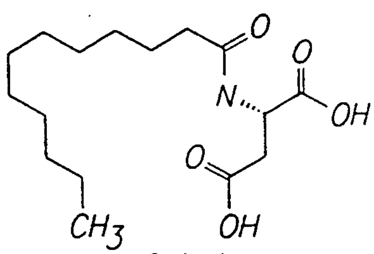
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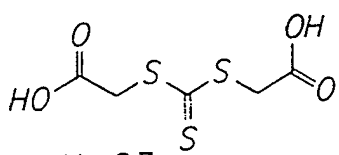
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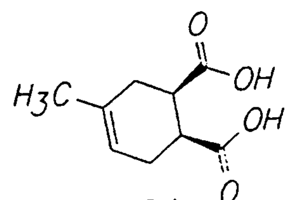
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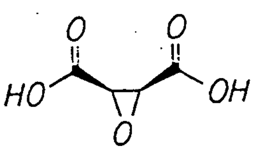
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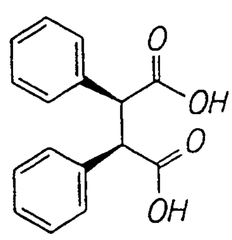
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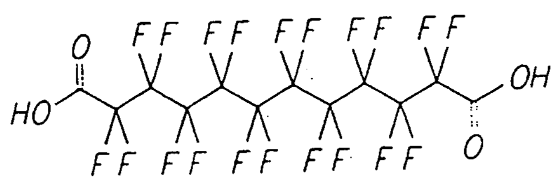
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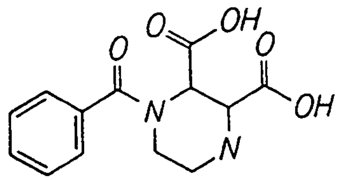

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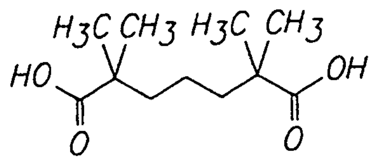

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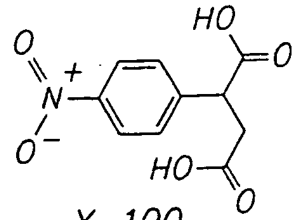

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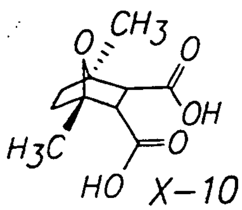

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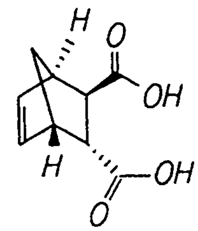

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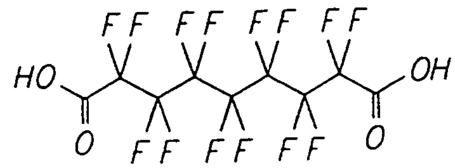

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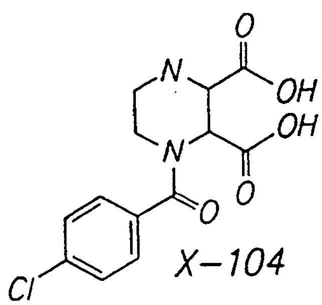

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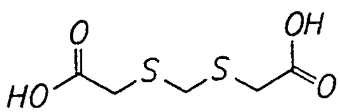

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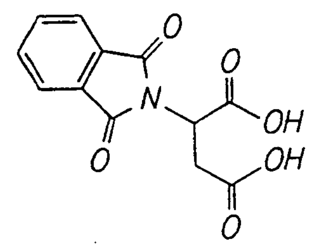

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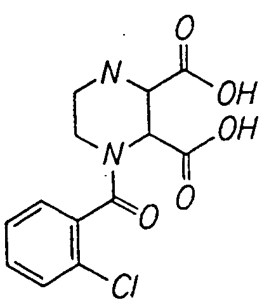

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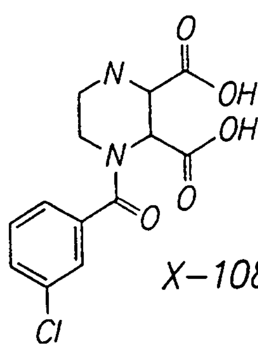

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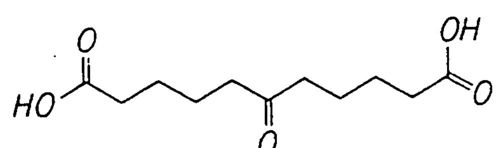

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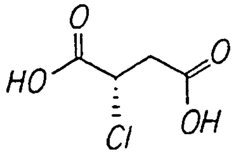

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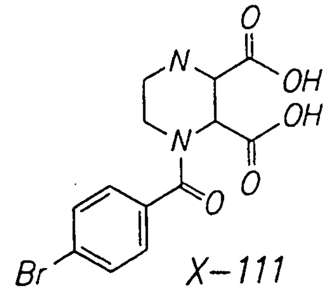

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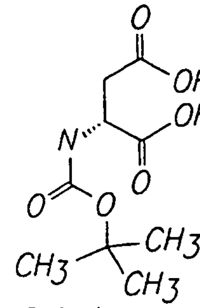

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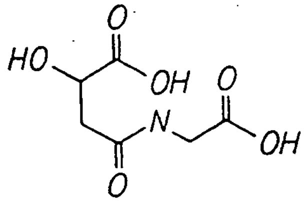

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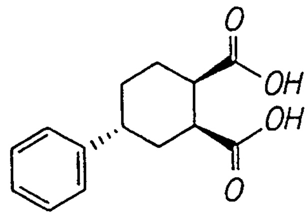

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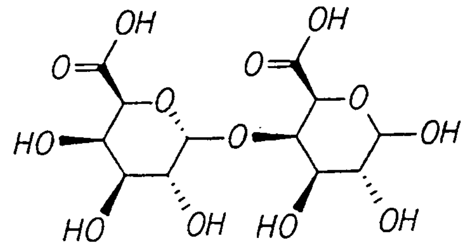

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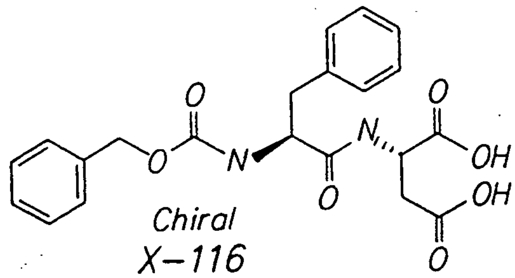

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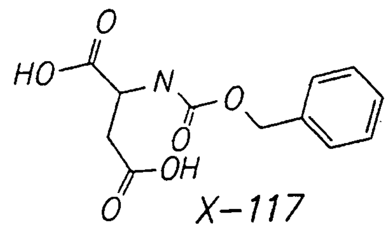

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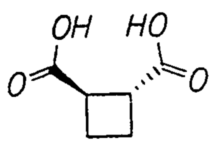

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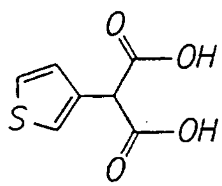

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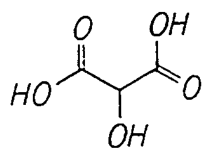

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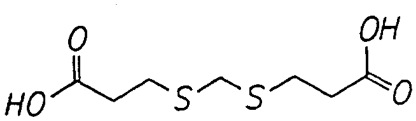

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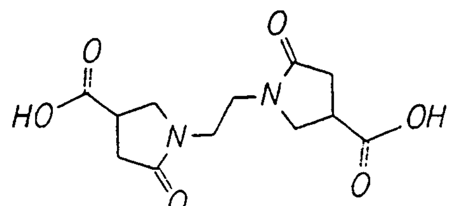

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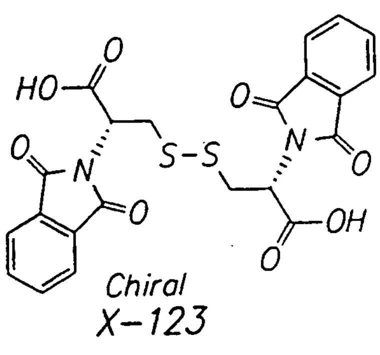

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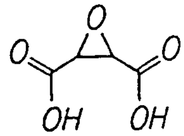

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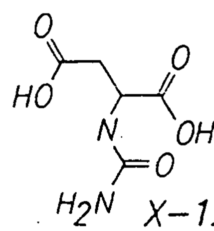

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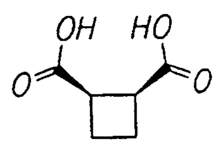

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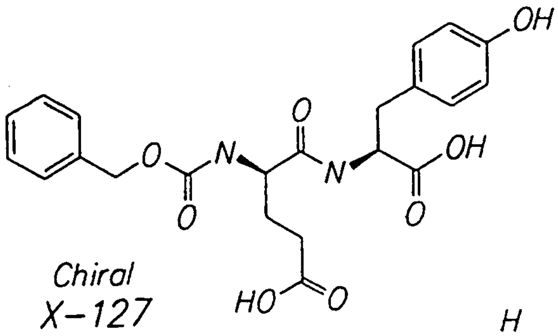

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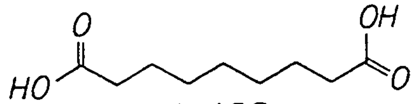

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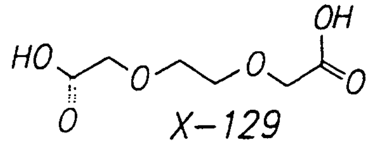

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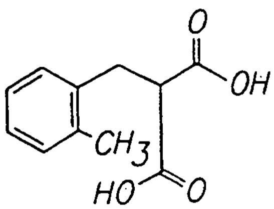

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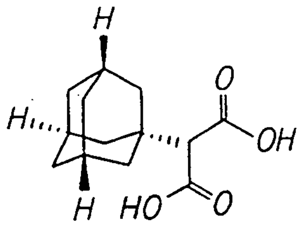

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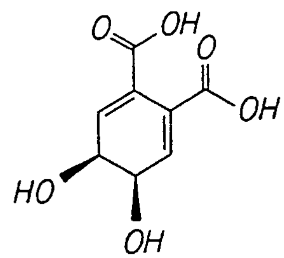

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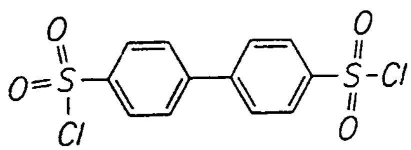
Disulfonyl Halides



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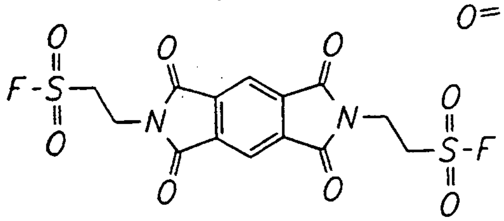

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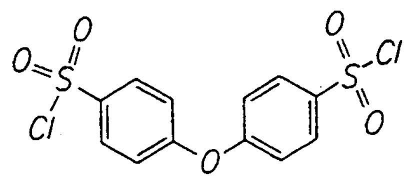

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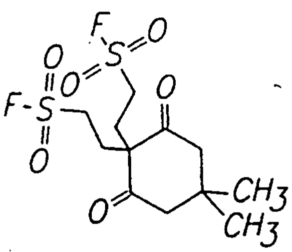

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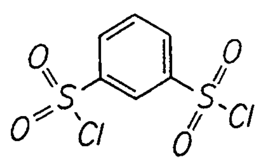

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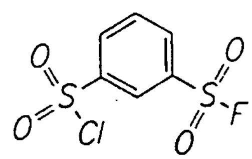

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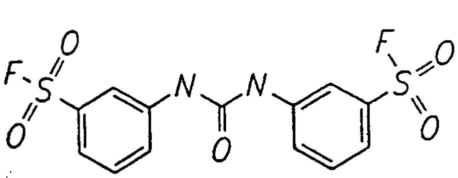

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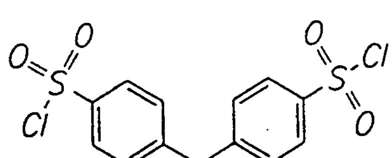

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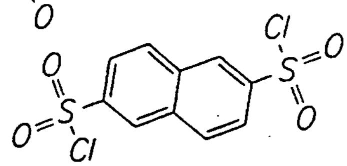

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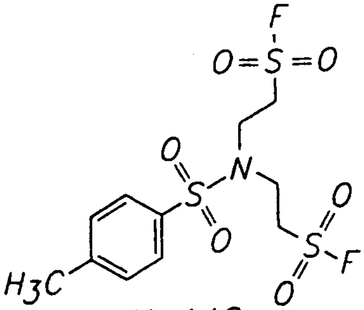

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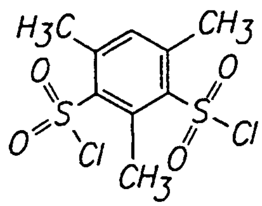

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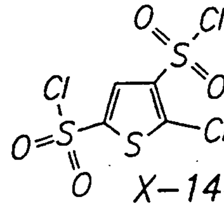

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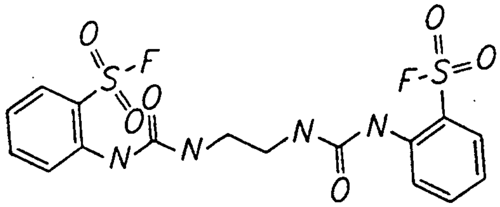

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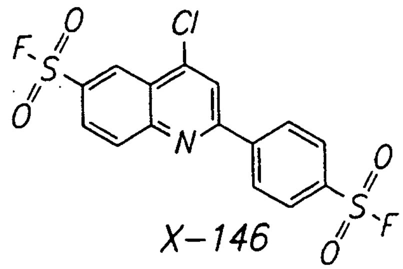

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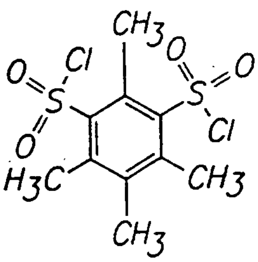

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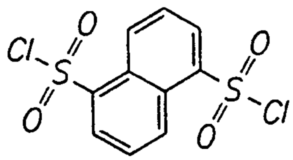

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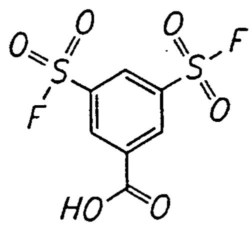

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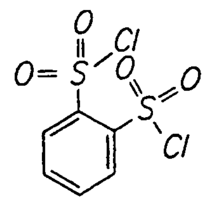

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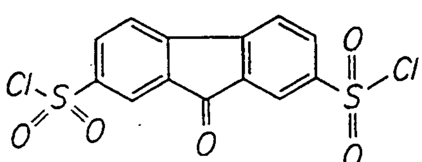

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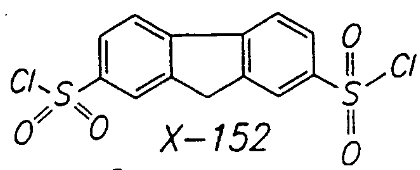

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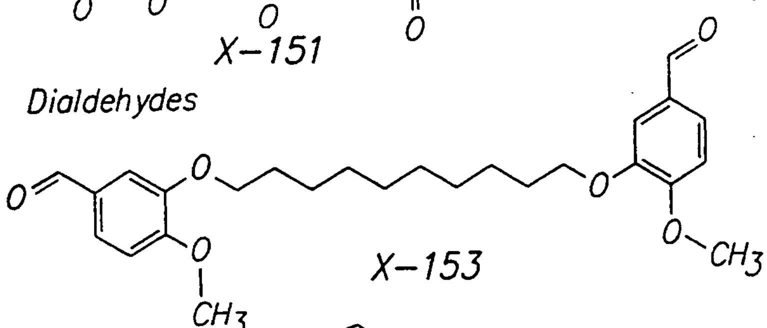
Dialdehydes



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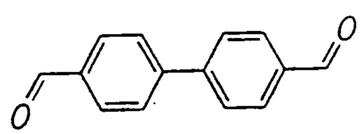

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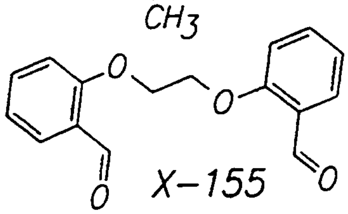

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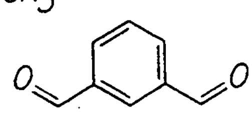

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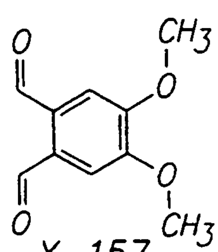

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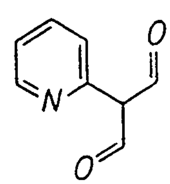

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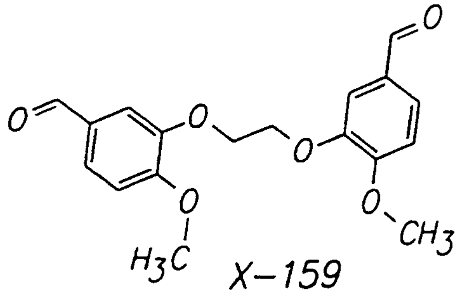
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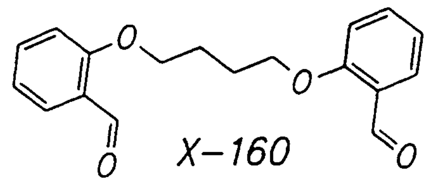
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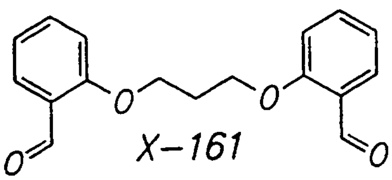
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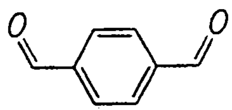
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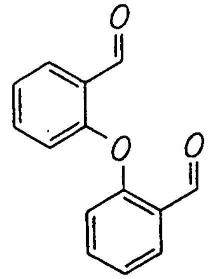
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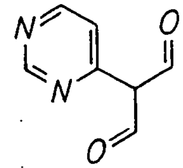
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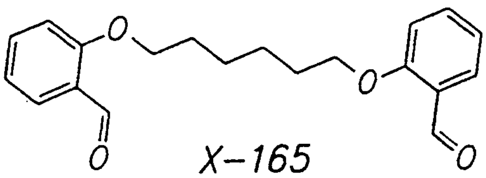
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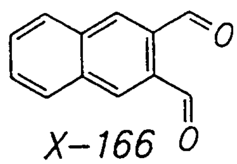
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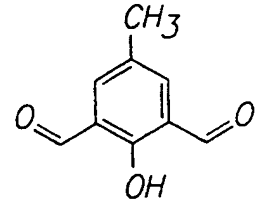
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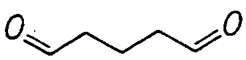
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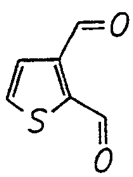
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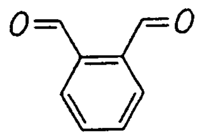
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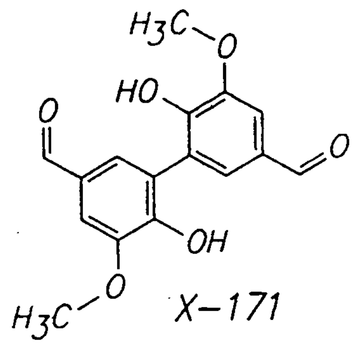
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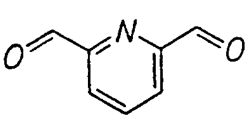
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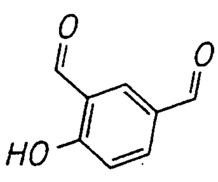
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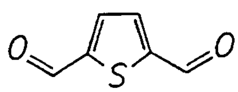
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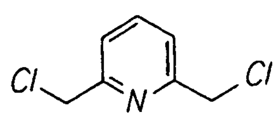
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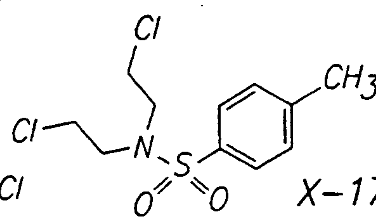
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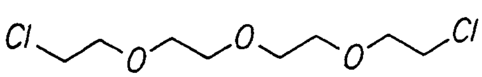
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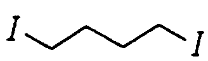
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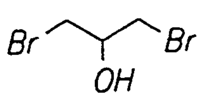
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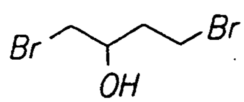
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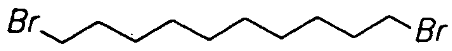
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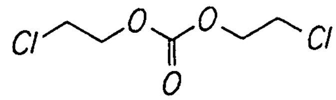
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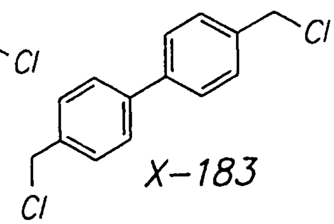
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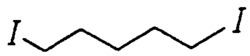
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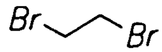
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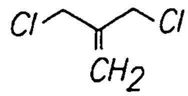
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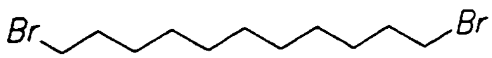
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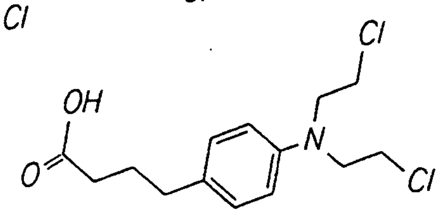
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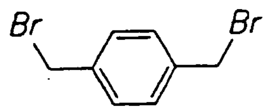
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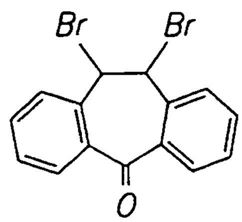
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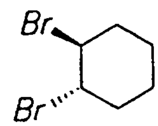
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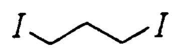
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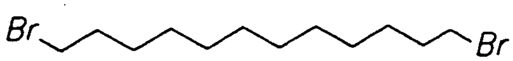
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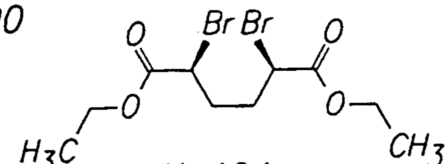
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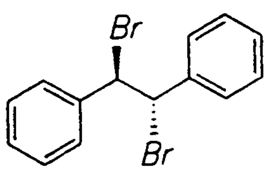
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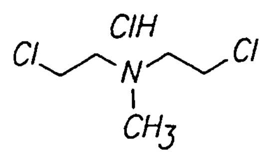
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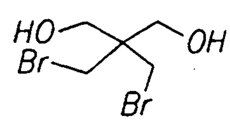
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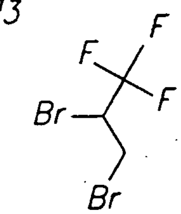
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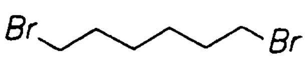
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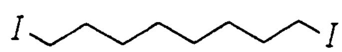
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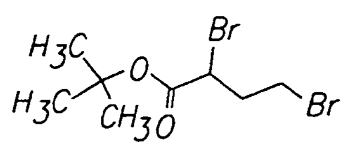
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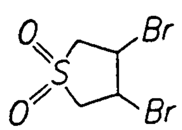
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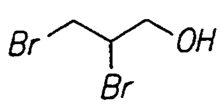
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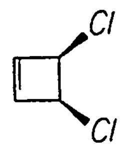
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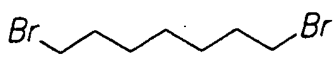
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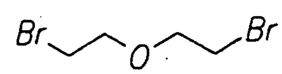
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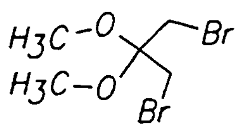
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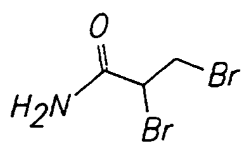
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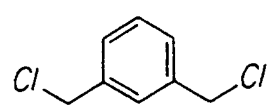
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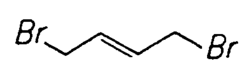
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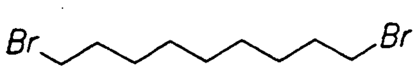
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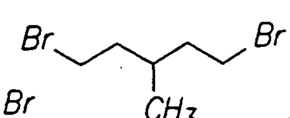
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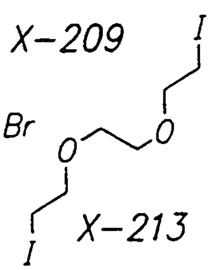
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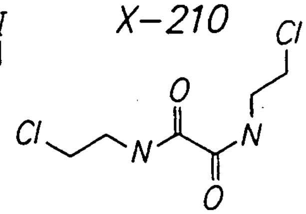
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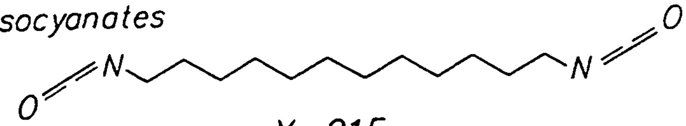

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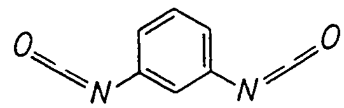

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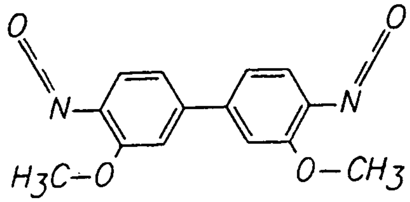

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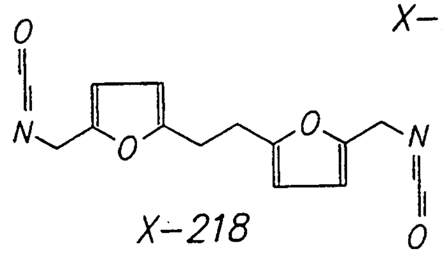

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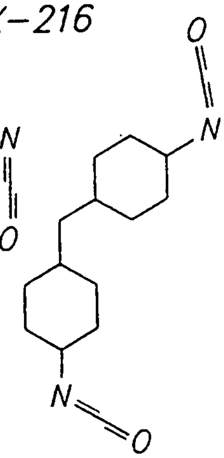

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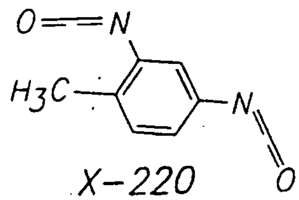

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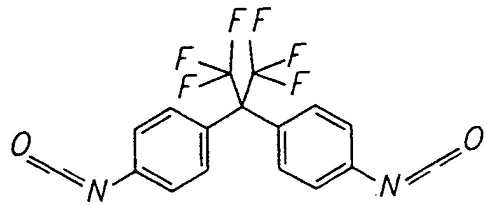

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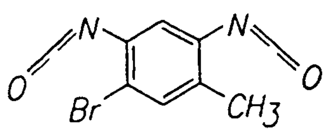

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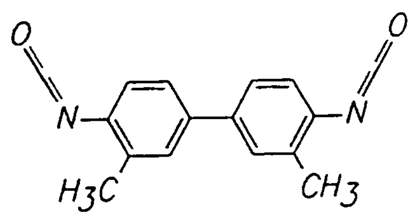

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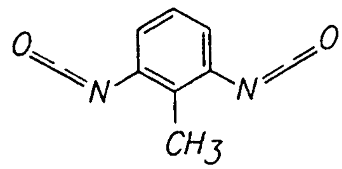

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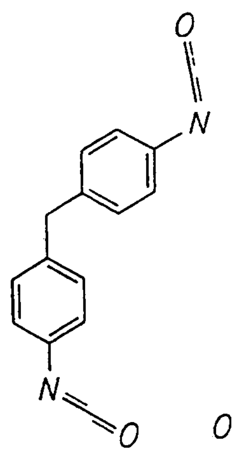

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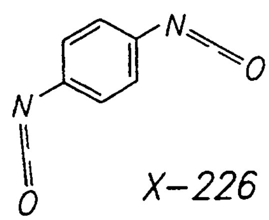

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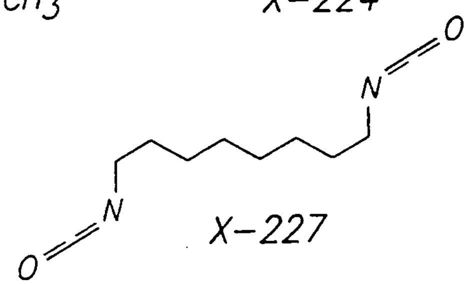

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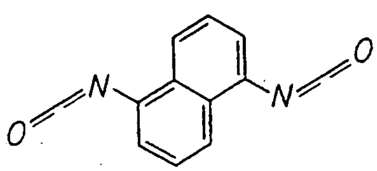

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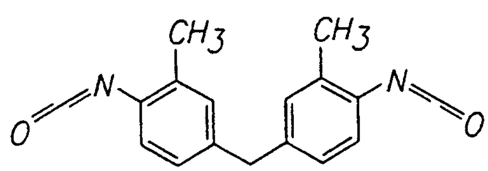

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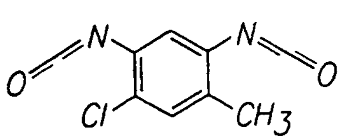

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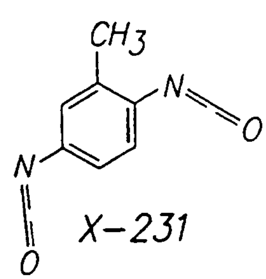

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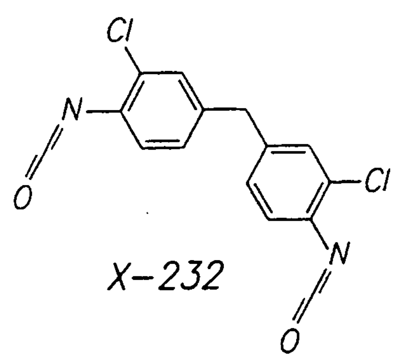

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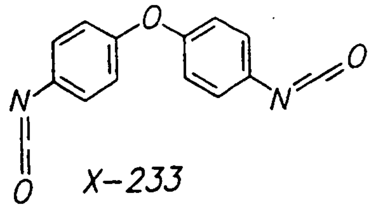

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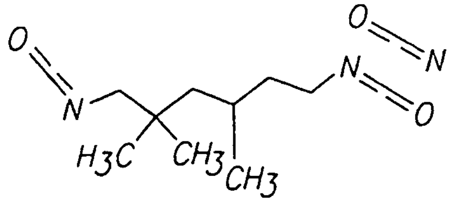

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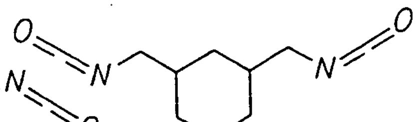

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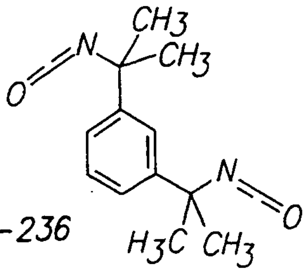

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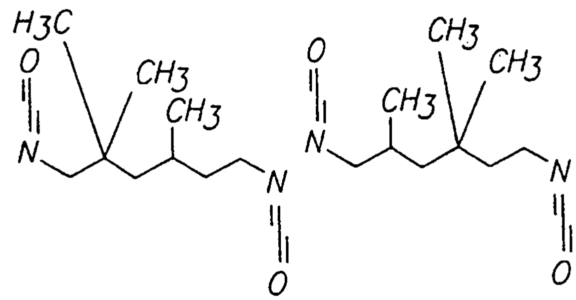

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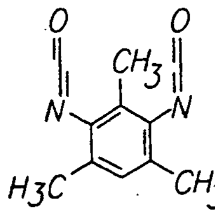

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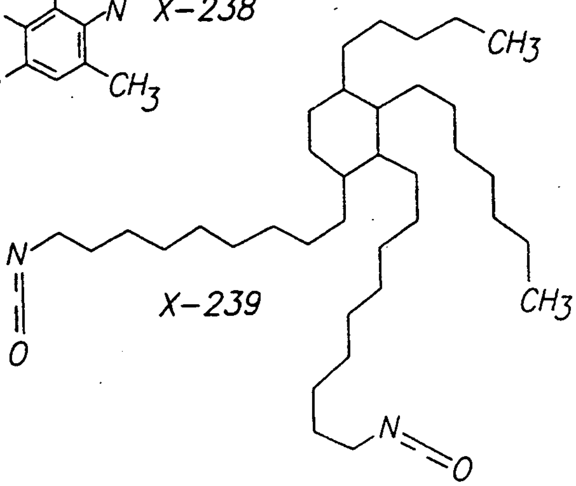

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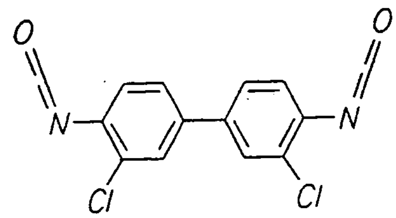

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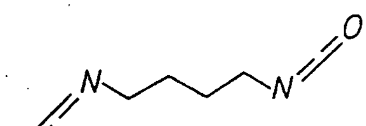

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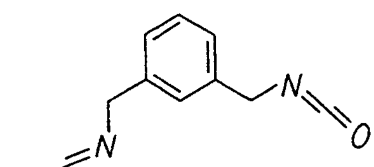

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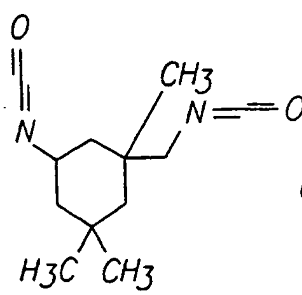

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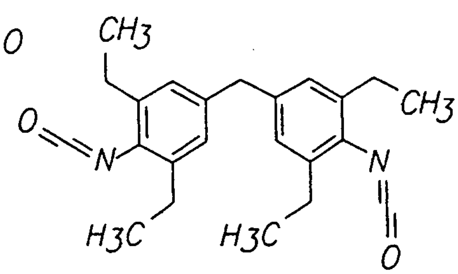

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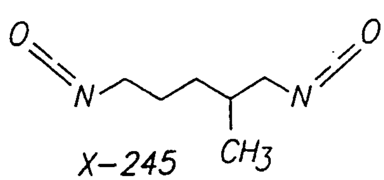

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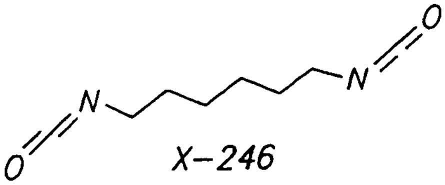

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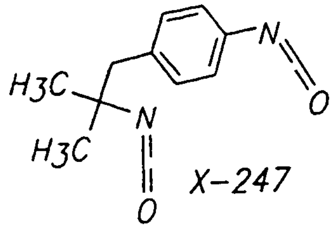

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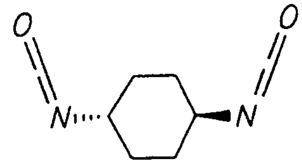

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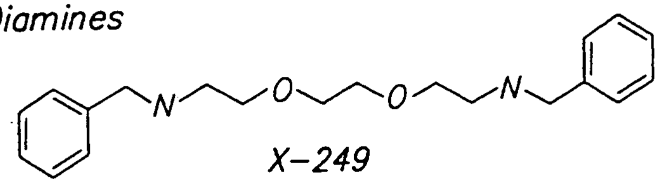

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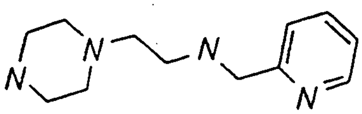

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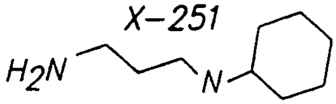

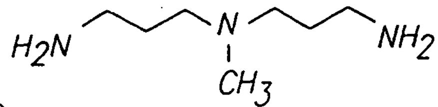

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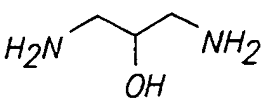

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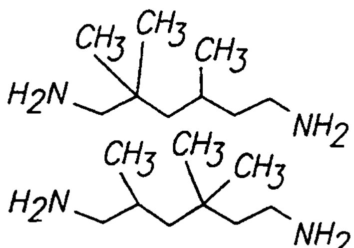

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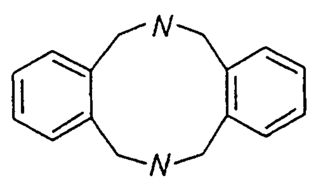

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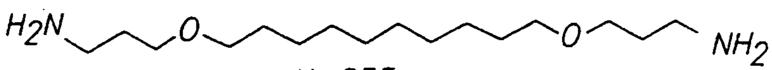

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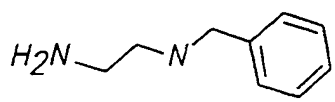

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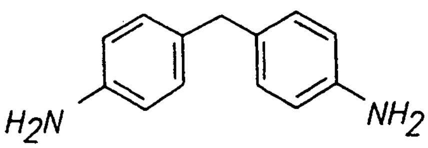

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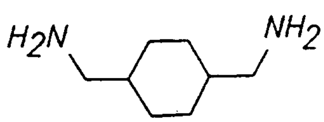

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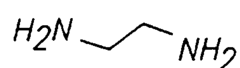

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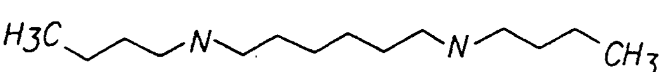

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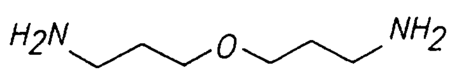

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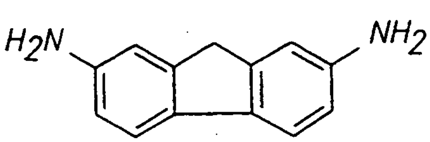

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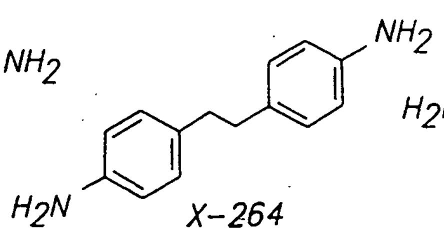

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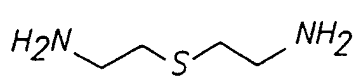

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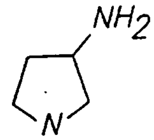
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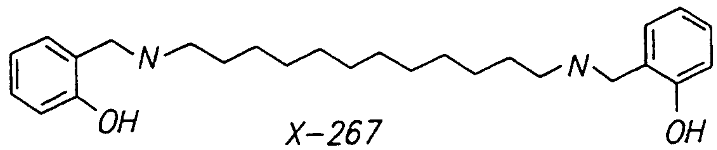
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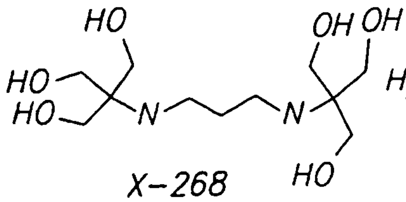
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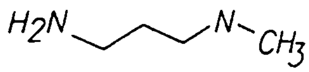
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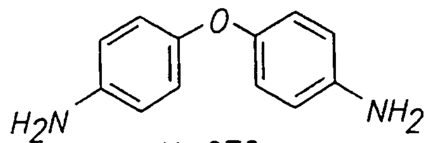
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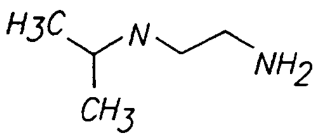
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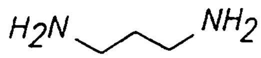
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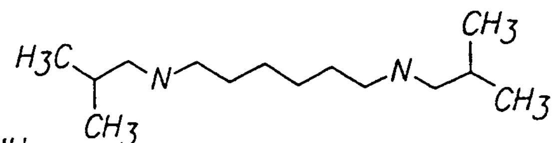
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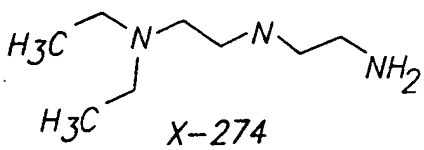
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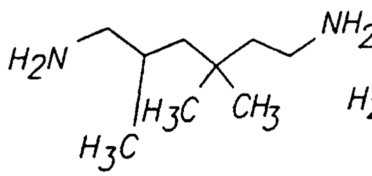
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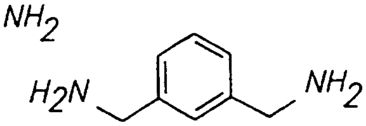
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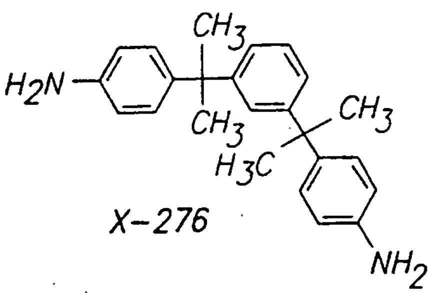
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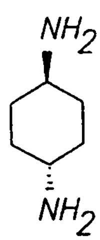
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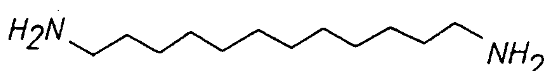
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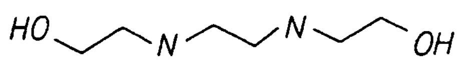
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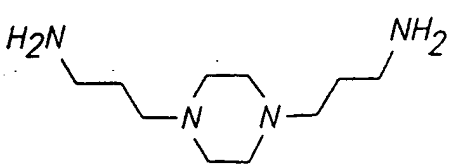
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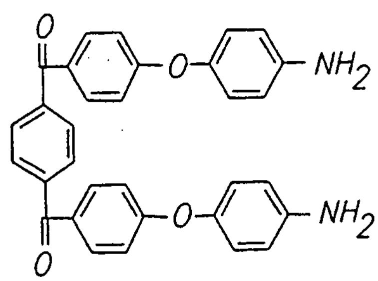
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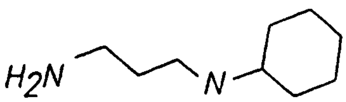
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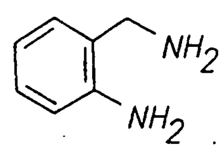
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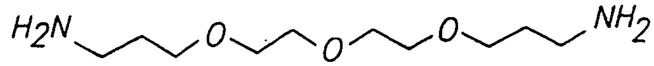

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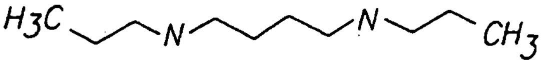

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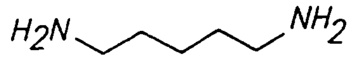

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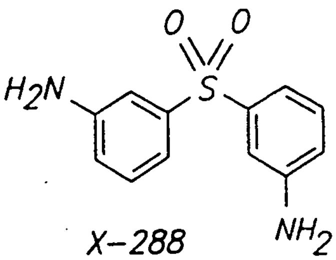

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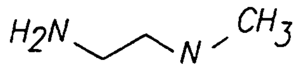

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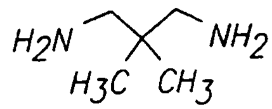

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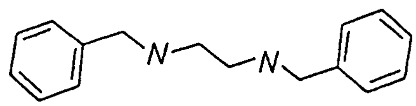

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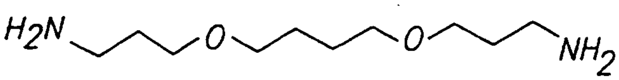

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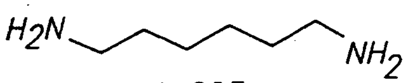

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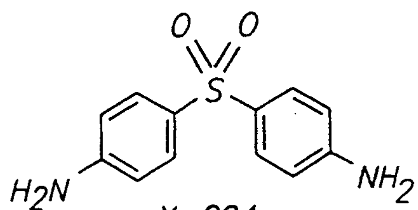

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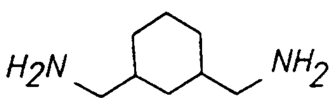

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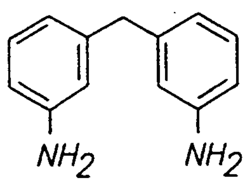

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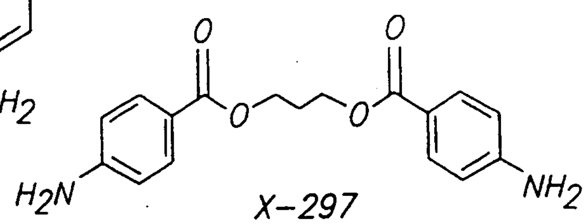

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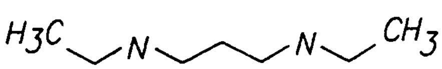

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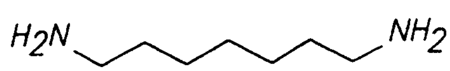

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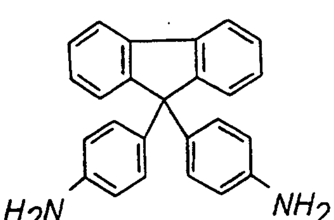

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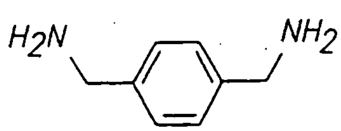

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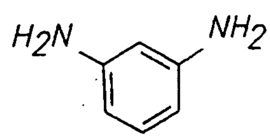

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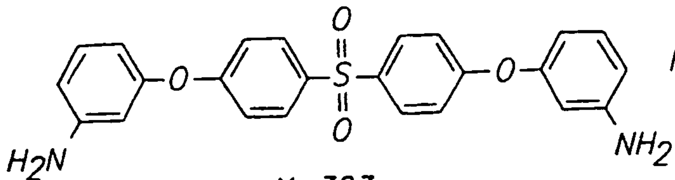

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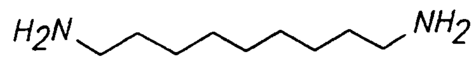

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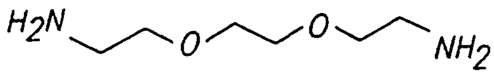

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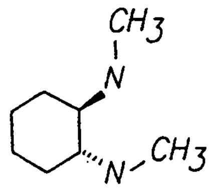

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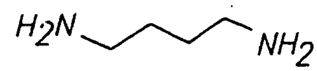

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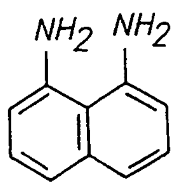

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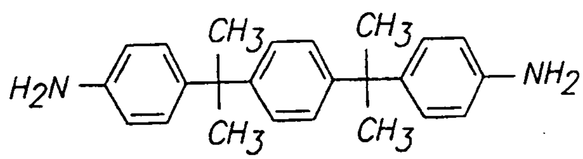

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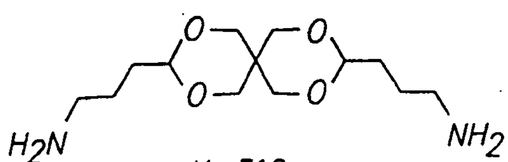

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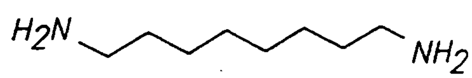

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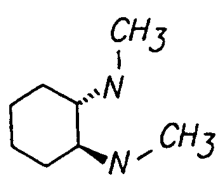

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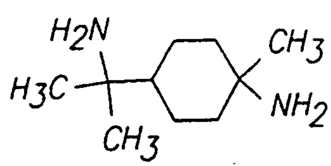

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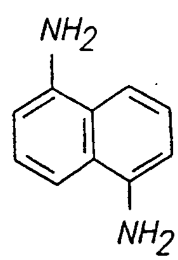

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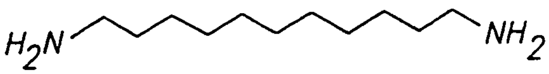

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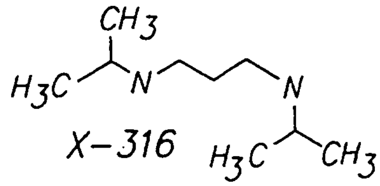

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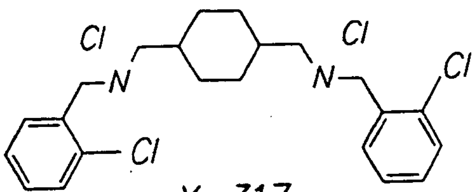

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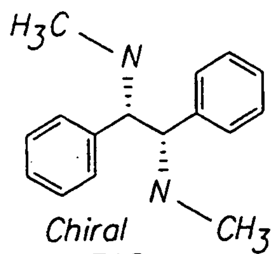

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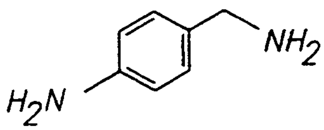

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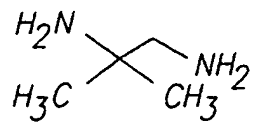

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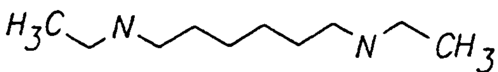

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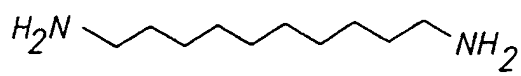

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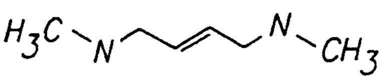

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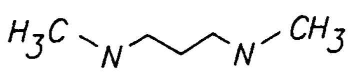

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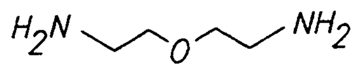

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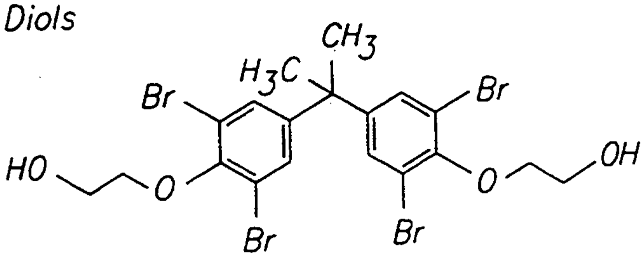

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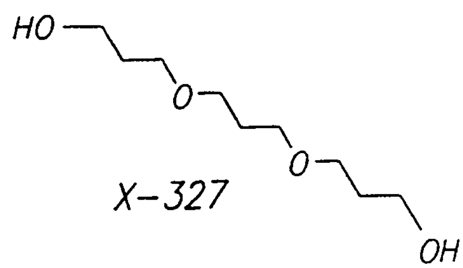

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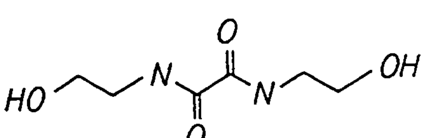

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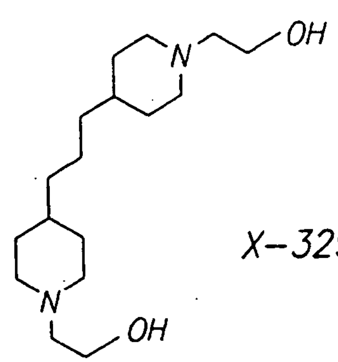

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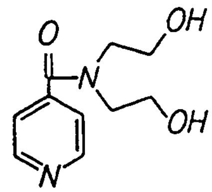

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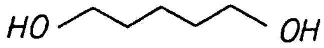

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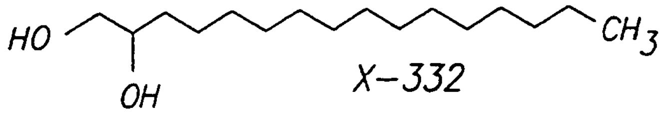

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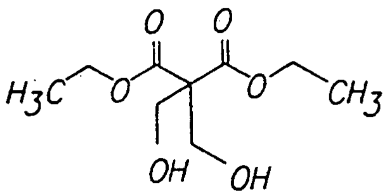

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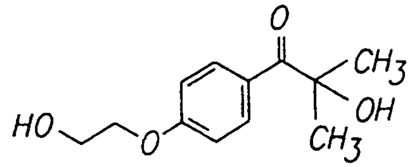

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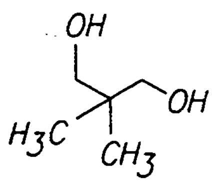

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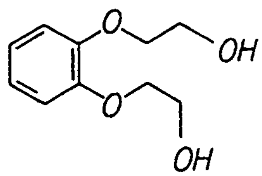

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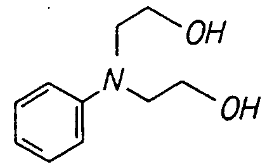

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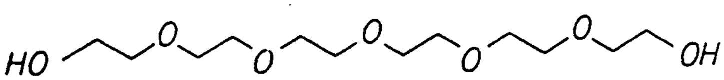

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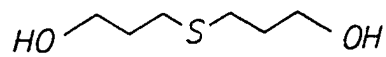

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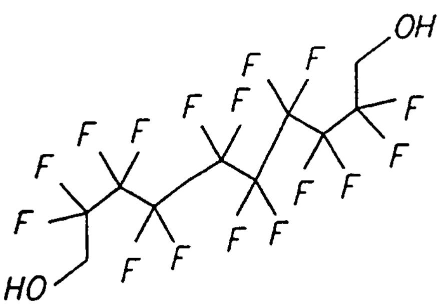

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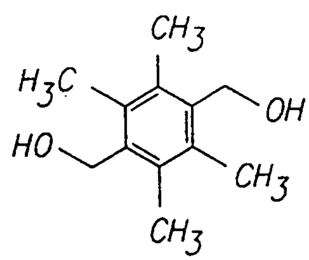

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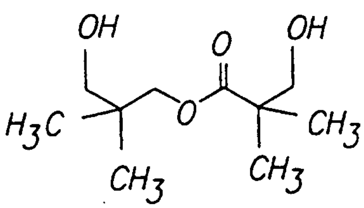

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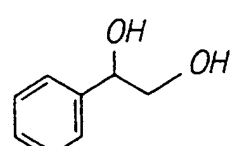

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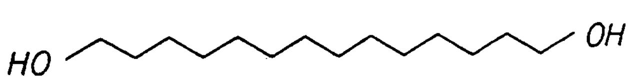

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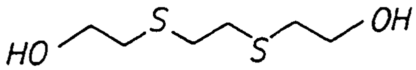
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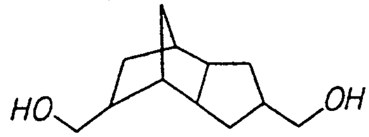
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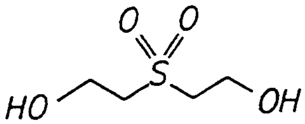
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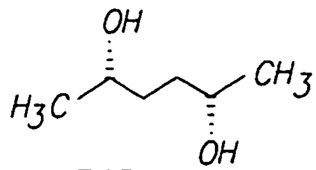
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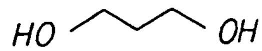
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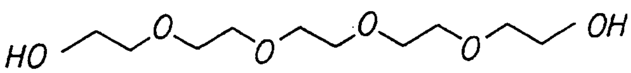
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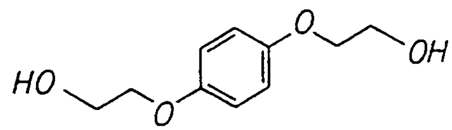
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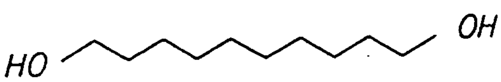
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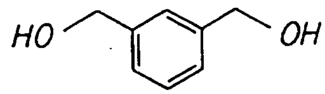
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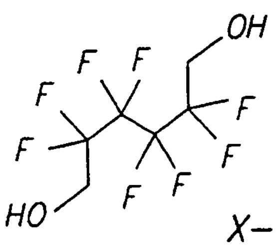
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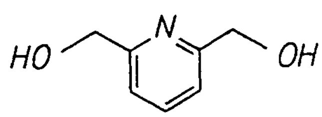
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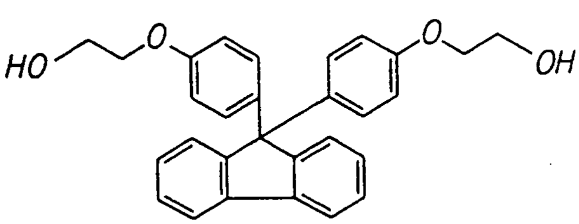
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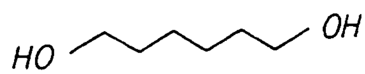
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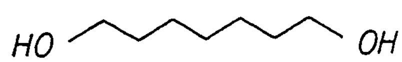
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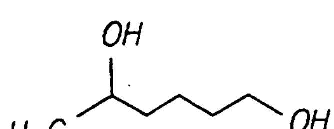
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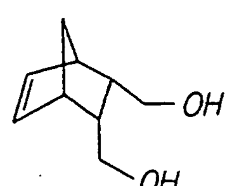
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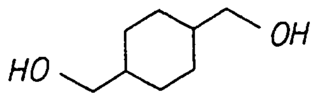
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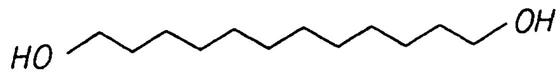
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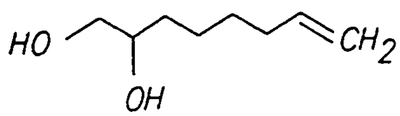
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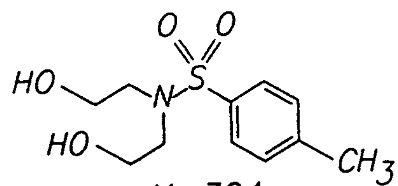
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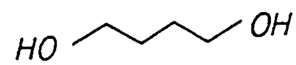
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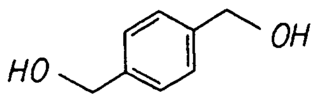
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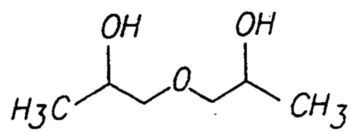
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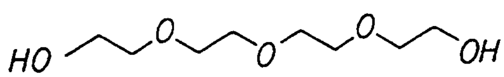
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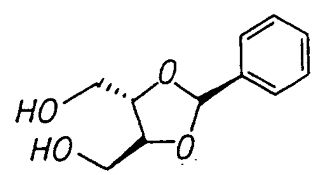
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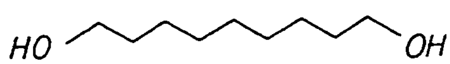
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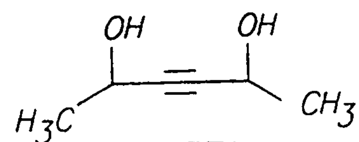
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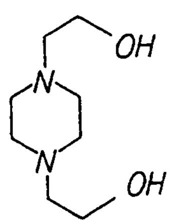

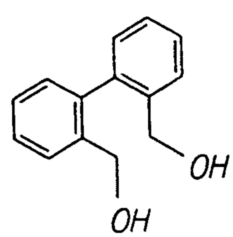
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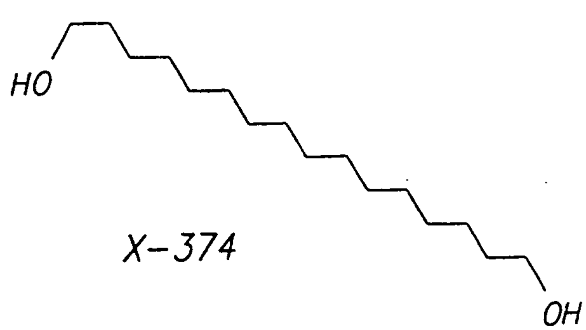
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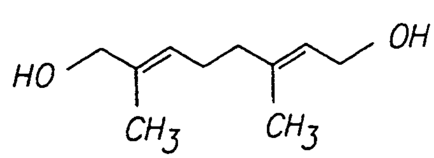
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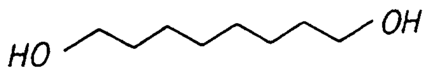

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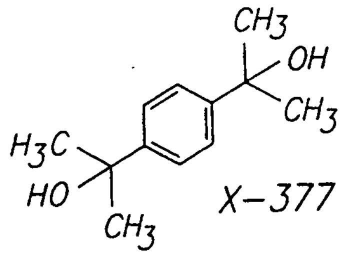

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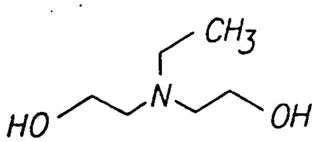
X-378



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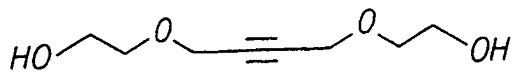

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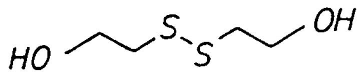

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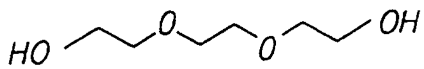

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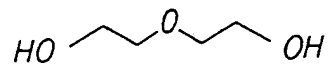

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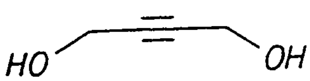

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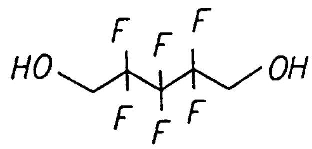
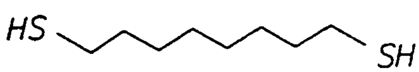


X-385

Dithiols



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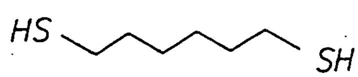

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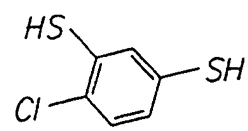

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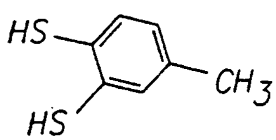

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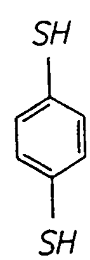

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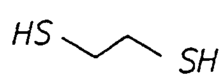

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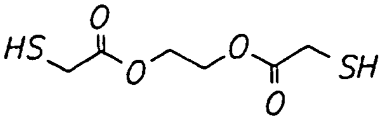
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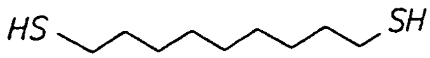
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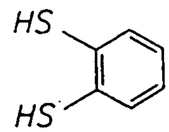
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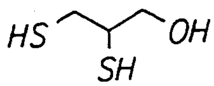
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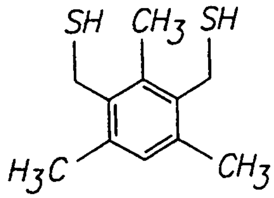
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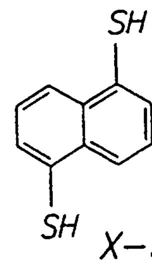
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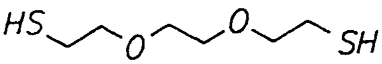
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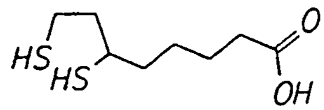
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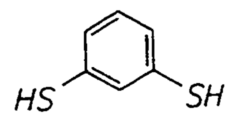
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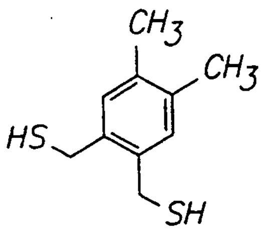
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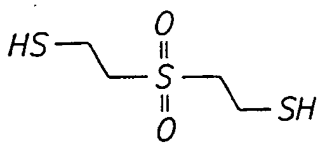
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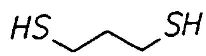
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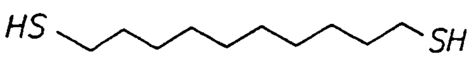
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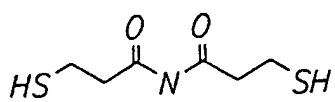
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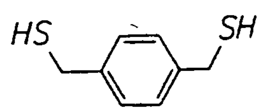
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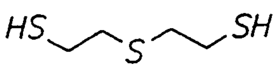
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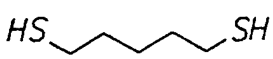
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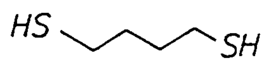
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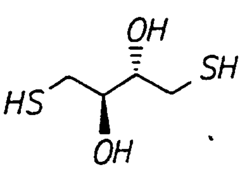
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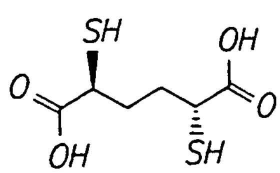
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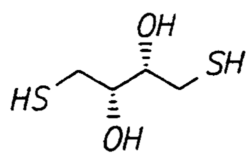
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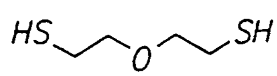
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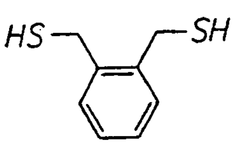
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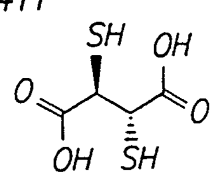
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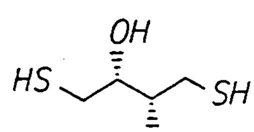
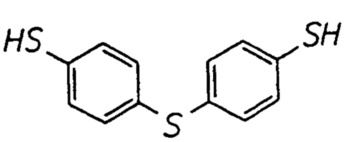

Chiral
X-416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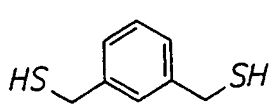
X-418

Representative ligands for use in this invention include, by way of example, L-1 through L-8 wherein L-1 is selected from a compound of formula (a) L-2 is selected from a compound of formula (b), L-3 is selected from a compound of formula (c), L-4 is selected from a compound of formula (d), L-5 is selected from a compound of formula (e), L-6 is selected from a compound of formula (f), L-7 is selected from a compound of formula (g), and L-8 is selected from a compound of formula (h) provided that at least one of the ligands is selected from ligands L-1 through L-5.

Combinations of ligands (L) and linkers (X) per this invention include, by way example only, homo- and hetero-dimers wherein a first ligand is selected from L-1 through L-5 and the second ligand and linker is selected from the following:

L-1/X-1-	L-1/X-2-	L-1/X-3-	L-1/X-4-	L-1/X-5-	L-1/X-6-
L-1/X-7-	L-1/X-8-	L-1/X-9-	L-1/X-10-	L-1/X-11-	L-1/X-12-
L-1/X-13-	L-1/X-14-	L-1/X-15-	L-1/X-16-	L-1/X-17-	L-1/X-18-
L-1/X-19-	L-1/X-20-	L-1/X-21-	L-1/X-22-	L-1/X-23-	L-1/X-24-
L-1/X-25-	L-1/X-26-	L-1/X-27-	L-1/X-28-	L-1/X-29-	L-1/X-30-
L-1/X-31-	L-1/X-32-	L-1/X-33-	L-1/X-34-	L-1/X-35-	L-1/X-36-
L-1/X-37-	L-1/X-38-	L-1/X-39-	L-1/X-40-	L-1/X-41-	L-1/X-42-
L-1/X-43-	L-1/X-44-	L-1/X-45-	L-1/X-46-	L-1/X-47-	L-1/X-48-
L-1/X-49-	L-1/X-50-	L-1/X-51-	L-1/X-52-	L-1/X-53-	L-1/X-54-
L-1/X-55-	L-1/X-56-	L-1/X-57-	L-1/X-58-	L-1/X-59-	L-1/X-60-
L-1/X-61-	L-1/X-62-	L-1/X-63-	L-1/X-64-	L-1/X-65-	L-1/X-66-
L-1/X-67-	L-1/X-68-	L-1/X-69-	L-1/X-70-	L-1/X-71-	L-1/X-72-
L-1/X-73-	L-1/X-74-	L-1/X-75-	L-1/X-76-	L-1/X-77-	L-1/X-78-
L-1/X-79-	L-1/X-80-	L-1/X-81-	L-1/X-82-	L-1/X-83-	L-1/X-84-
L-1/X-85-	L-1/X-86-	L-1/X-87-	L-1/X-88-	L-1/X-89-	L-1/X-90-
L-1/X-91-	L-1/X-92-	L-1/X-93-	L-1/X-94-	L-1/X-95-	L-1/X-96-
L-1/X-97-	L-1/X-98-	L-1/X-99-	L-1/X-100-	L-1/X-101-	L-1/X-102-
L-1/X-103-	L-1/X-104-	L-1/X-105-	L-1/X-106-	L-1/X-107-	L-1/X-108-
L-1/X-109-	L-1/X-110-	L-1/X-111-	L-1/X-112-	L-1/X-113-	L-1/X-114-
L-1/X-115-	L-1/X-116-	L-1/X-117-	L-1/X-118-	L-1/X-119-	L-1/X-120-
L-1/X-121-	L-1/X-122-	L-1/X-123-	L-1/X-124-	L-1/X-125-	L-1/X-126-

L-1/X-127-	L-1/X-128-	L-1/X-129-	L-1/X-130-	L-1/X-131-	L-1/X-132-
L-1/X-133-	L-1/X-134-	L-1/X-135-	L-1/X-136-	L-1/X-137-	L-1/X-138-
L-1/X-139-	L-1/X-140-	L-1/X-141-	L-1/X-142-	L-1/X-143-	L-1/X-144-
L-1/X-145-	L-1/X-146-	L-1/X-147-	L-1/X-148-	L-1/X-149-	L-1/X-150-
L-1/X-151-	L-1/X-152-	L-1/X-153-	L-1/X-154-	L-1/X-155-	L-1/X-156-
L-1/X-157-	L-1/X-158-	L-1/X-159-	L-1/X-160-	L-1/X-161-	L-1/X-162-
L-1/X-163-	L-1/X-164-	L-1/X-165-	L-1/X-166-	L-1/X-167-	L-1/X-168-
L-1/X-169-	L-1/X-170-	L-1/X-171-	L-1/X-172-		
L-1/X-173-	L-1/X-174-	L-1/X-175-	L-1/X-176-	L-1/X-177-	L-1/X-178-
L-1/X-179-	L-1/X-180-	L-1/X-181-	L-1/X-182-	L-1/X-183-	L-1/X-184-
L-1/X-185-	L-1/X-186-	L-1/X-187-	L-1/X-188-	L-1/X-189-	L-1/X-190-
L-1/X-191-	L-1/X-192-	L-1/X-193-	L-1/X-194-	L-1/X-195-	L-1/X-196-
L-1/X-197-	L-1/X-198-	L-1/X-199-	L-1/X-200-	L-1/X-201-	L-1/X-202-
L-1/X-203-	L-1/X-204-	L-1/X-205-	L-1/X-206-	L-1/X-207-	L-1/X-208-
L-1/X-209-	L-1/X-210-	L-1/X-211-	L-1/X-212-	L-1/X-213-	L-1/X-214-
L-1/X-215-	L-1/X-216-	L-1/X-217-	L-1/X-218-	L-1/X-219-	L-1/X-220-
L-1/X-221-	L-1/X-222-	L-1/X-223-	L-1/X-224-	L-1/X-225-	L-1/X-226-
L-1/X-227-	L-1/X-228-	L-1/X-229-	L-1/X-230-	L-1/X-231-	L-1/X-232-
L-1/X-233-	L-1/X-234-	L-1/X-235-	L-1/X-236-	L-1/X-237-	L-1/X-238-
L-1/X-239-	L-1/X-240-	L-1/X-241-	L-1/X-242-	L-1/X-243-	L-1/X-244-
L-1/X-245-	L-1/X-246-	L-1/X-247-	L-1/X-248-	L-1/X-249-	L-1/X-250-
L-1/X-251-	L-1/X-252-	L-1/X-253-	L-1/X-254-	L-1/X-255-	L-1/X-256-
L-1/X-257-	L-1/X-258-	L-1/X-259-	L-1/X-260-	L-1/X-261-	L-1/X-262-
L-1/X-263-	L-1/X-264-	L-1/X-265-	L-1/X-266-	L-1/X-267-	L-1/X-268-
L-1/X-269-	L-1/X-270-	L-1/X-271-	L-1/X-272-	L-1/X-273-	L-1/X-274-
L-1/X-275-	L-1/X-276-	L-1/X-277-	L-1/X-278-	L-1/X-279-	L-1/X-280-
L-1/X-281-	L-1/X-282-	L-1/X-283-	L-1/X-284-	L-1/X-285-	L-1/X-286-
L-1/X-287-	L-1/X-288-	L-1/X-289-	L-1/X-290-	L-1/X-291-	L-1/X-292-
L-1/X-293-	L-1/X-294-	L-1/X-295-	L-1/X-296-	L-1/X-297-	L-1/X-298-
L-1/X-299-	L-1/X-300-	L-1/X-301-	L-1/X-302-	L-1/X-303-	L-1/X-304-
L-1/X-305-	L-1/X-306-	L-1/X-307-	L-1/X-308-	L-1/X-309-	L-1/X-310-
L-1/X-311-	L-1/X-312-	L-1/X-313-	L-1/X-314-	L-1/X-315-	L-1/X-316-
L-1/X-317-	L-1/X-318-	L-1/X-319-	L-1/X-320-	L-1/X-321-	L-1/X-322-
L-1/X-323-	L-1/X-324-	L-1/X-325-	L-1/X-326-	L-1/X-327-	L-1/X-328-
L-1/X-329-	L-1/X-330-	L-1/X-331-	L-1/X-332-	L-1/X-333-	L-1/X-334-

L-1/X-335-	L-1/X-336-	L-1/X-337-	L-1/X-338-	L-1/X-339-	L-1/X-340-
L-1/X-341-	L-1/X-342-	L-1/X-343-	L-1/X-344-	L-1/X-345-	L-1/X-346-
L-1/X-347-	L-1/X-348-	L-1/X-349-	L-1/X-350-	L-1/X-351-	L-1/X-352-
L-1/X-353-	L-1/X-354-	L-1/X-355-	L-1/X-356-	L-1/X-357-	L-1/X-358-
L-1/X-359-	L-1/X-360-	L-1/X-361-	L-1/X-362-	L-1/X-363-	L-1/X-364-
L-1/X-365-	L-1/X-366-	L-1/X-367-	L-1/X-368-	L-1/X-369-	L-1/X-370-
L-1/X-371-	L-1/X-372-	L-1/X-373-	L-1/X-374-	L-1/X-375-	L-1/X-376-
L-1/X-377-	L-1/X-378-	L-1/X-379-	L-1/X-380-	L-1/X-381-	L-1/X-382-
L-1/X-383-	L-1/X-384-	L-1/X-385-	L-1/X-386-	L-1/X-387-	L-1/X-388-
L-1/X-389-	L-1/X-390-	L-1/X-391-	L-1/X-392-	L-1/X-393-	L-1/X-394-
L-1/X-395-	L-1/X-396-	L-1/X-397-	L-1/X-398-	L-1/X-399-	L-1/X-400-
L-1/X-401-	L-1/X-402-	L-1/X-403-	L-1/X-404-	L-1/X-405-	L-1/X-406-
L-1/X-407-	L-1/X-408-	L-1/X-409-	L-1/X-410-	L-1/X-411-	L-1/X-412-
L-1/X-413-	L-1/X-414-	L-1/X-415-	L-1/X-416-	L-1/X-417-	L-1/X-418-

L-2/X-1-	L-2/X-2-	L-2/X-3-	L-2/X-4-	L-2/X-5-	L-2/X-6-
L-2/X-7-	L-2/X-8-	L-2/X-9-	L-2/X-10-	L-2/X-11-	L-2/X-12-
L-2/X-13-	L-2/X-14-	L-2/X-15-	L-2/X-16-	L-2/X-17-	L-2/X-18-
L-2/X-19-	L-2/X-20-	L-2/X-21-	L-2/X-22-	L-2/X-23-	L-2/X-24-
L-2/X-25-	L-2/X-26-	L-2/X-27-	L-2/X-28-	L-2/X-29-	L-2/X-30-
L-2/X-31-	L-2/X-32-	L-2/X-33-	L-2/X-34-	L-2/X-35-	L-2/X-36-
L-2/X-37-	L-2/X-38-	L-2/X-39-	L-2/X-40-	L-2/X-41-	L-2/X-42-
L-2/X-43-	L-2/X-44-	L-2/X-45-	L-2/X-46-	L-2/X-47-	L-2/X-48-
L-2/X-49-	L-2/X-50-	L-2/X-51-	L-2/X-52-	L-2/X-53-	L-2/X-54-
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L-2/X-73-	L-2/X-74-	L-2/X-75-	L-2/X-76-	L-2/X-77-	L-2/X-78-
L-2/X-79-	L-2/X-80-	L-2/X-81-	L-2/X-82-	L-2/X-83-	L-2/X-84-
L-2/X-85-	L-2/X-86-	L-2/X-87-	L-2/X-88-	L-2/X-89-	L-2/X-90-
L-2/X-91-	L-2/X-92-	L-2/X-93-	L-2/X-94-	L-2/X-95-	L-2/X-96-
L-2/X-97-	L-2/X-98-	L-2/X-99-	L-2/X-100-	L-2/X-101-	L-2/X-102-
L-2/X-103-	L-2/X-104-	L-2/X-105-	L-2/X-106-	L-2/X-107-	L-2/X-108-
L-2/X-109-	L-2/X-110-	L-2/X-111-	L-2/X-112-	L-2/X-113-	L-2/X-114-

L-2/X-115-	L-2/X-116-	L-2/X-117-	L-2/X-118-	L-2/X-119-	L-2/X-120-
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L-2/X-133-	L-2/X-134-	L-2/X-135-	L-2/X-136-	L-2/X-137-	L-2/X-138-
L-2/X-139-	L-2/X-140-	L-2/X-141-	L-2/X-142-	L-2/X-143-	L-2/X-144-
L-2/X-145-	L-2/X-146-	L-2/X-147-	L-2/X-148-	L-2/X-149-	L-2/X-150-
L-2/X-151-	L-2/X-152-	L-2/X-153-	L-2/X-154-	L-2/X-155-	L-2/X-156-
L-2/X-157-	L-2/X-158-	L-2/X-159-	L-2/X-160-	L-2/X-161-	L-2/X-162-
L-2/X-163-	L-2/X-164-	L-2/X-165-	L-2/X-166-	L-2/X-167-	L-2/X-168-
L-2/X-169-	L-2/X-170-	L-2/X-171-	L-2/X-172-		
L-2/X-173-	L-2/X-174-	L-2/X-175-	L-2/X-176-	L-2/X-177-	L-2/X-178-
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L-2/X-191-	L-2/X-192-	L-2/X-193-	L-2/X-194-	L-2/X-195-	L-2/X-196-
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L-2/X-269-	L-2/X-270-	L-2/X-271-	L-2/X-272-	L-2/X-273-	L-2/X-274-
L-2/X-275-	L-2/X-276-	L-2/X-277-	L-2/X-278-	L-2/X-279-	L-2/X-280-
L-2/X-281-	L-2/X-282-	L-2/X-283-	L-2/X-284-	L-2/X-285-	L-2/X-286-
L-2/X-287-	L-2/X-288-	L-2/X-289-	L-2/X-290-	L-2/X-291-	L-2/X-292-
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L-2/X-377-	L-2/X-378-	L-2/X-379-	L-2/X-380-	L-2/X-381-	L-2/X-382-
L-2/X-383-	L-2/X-384-	L-2/X-385-	L-2/X-386-	L-2/X-387-	L-2/X-388-
L-2/X-389-	L-2/X-390-	L-2/X-391-	L-2/X-392-	L-2/X-393-	L-2/X-394-
L-2/X-395-	L-2/X-396-	L-2/X-397-	L-2/X-398-	L-2/X-399-	L-2/X-400-
L-2/X-401-	L-2/X-402-	L-2/X-403-	L-2/X-404-	L-2/X-405-	L-2/X-406-
L-2/X-407-	L-2/X-408-	L-2/X-409-	L-2/X-410-	L-2/X-411-	L-2/X-412-
L-2/X-413-	L-2/X-414-	L-2/X-415-	L-2/X-416-	L-2/X-417-	L-2/X-418-

and so on, substituting L-2 with L-3 through L-8.

Utility, Testing, and Administration

Utility

The multibinding compounds of this invention are muscarinic receptor antagonists, in particular M_3 muscarinic receptor antagonists. Accordingly, the multibinding compounds and pharmaceutical compositions of this invention are useful in the treatment and prevention of diseases mediated by these receptors such as chronic obstructive pulmonary disease, chronic bronchitis, irritable bowel syndrome, urinary incontinence, and the like.

Testing

The ability of the compounds of formula (I) to inhibit a muscarinic receptor, such as M_3 subtype may be demonstrated by a variety of *in vitro* assays and *in vivo* assays described in Examples 19-24.

Pharmaceutical Formulations

When employed as pharmaceuticals, the compounds of this invention are usually administered in the form of pharmaceutical compositions. These compounds can be administered by a variety of routes including oral, rectal, transdermal, subcutaneous, intravenous, intramuscular, and intranasal. These compounds are effective as both injectable and oral compositions. Such compositions are prepared in a manner well known in the pharmaceutical art and comprise at least one active compound.

This invention also includes pharmaceutical compositions which contain, as the active ingredient, one or more of the compounds described herein associated with pharmaceutically acceptable carriers. In making the compositions of this invention, the active ingredient is usually mixed with an excipient, diluted by an excipient or enclosed within such a carrier which can be in the form of a capsule, sachet, paper or other container. When the excipient serves as a diluent, it can be a solid, semi-solid, or liquid material, which acts as a vehicle, carrier or medium for the active ingredient. Thus, the compositions can be in the form of tablets, pills, powders, lozenges, sachets, cachets, elixirs, suspensions, emulsions, solutions, syrups, aerosols (as a solid or in a liquid medium), ointments containing, for example, up to 10% by weight of the active compound, soft and hard gelatin capsules, suppositories, sterile injectable solutions, and sterile packaged powders.

In preparing a formulation, it may be necessary to mill the active compound to provide the appropriate particle size prior to combining with the other ingredients. If the active compound is substantially insoluble, it ordinarily is milled to a particle size of less than 200 mesh. If the active compound is substantially water soluble, the particle size is normally adjusted by milling to provide a substantially uniform distribution in the formulation, e.g. about 40 mesh.

Some examples of suitable excipients include lactose, dextrose, sucrose, sorbitol, mannitol, starches, gum acacia, calcium phosphate, alginates, tragacanth, gelatin, calcium silicate, microcrystalline cellulose, polyvinylpyrrolidone, cellulose, sterile water, syrup, and methyl cellulose. The formulations can additionally

include: lubricating agents such as talc, magnesium stearate, and mineral oil; wetting agents; emulsifying and suspending agents; preserving agents such as methyl- and propylhydroxy-benzoates; sweetening agents; and flavoring agents. The compositions of the invention can be formulated so as to provide quick, sustained or delayed release of the active ingredient after administration to the patient by employing procedures known in the art.

The compositions are preferably formulated in a unit dosage form, each dosage containing from about 0.001 to about 1 g, more usually about 1 to about 30 mg, of the active ingredient. The term "unit dosage forms" refers to physically discrete units suitable as unitary dosages for human subjects and other mammals, each unit containing a predetermined quantity of active material calculated to produce the desired therapeutic effect, in association with a suitable pharmaceutical excipient. Preferably, the compound of Formula (I) above is employed at no more than about 20 weight percent of the pharmaceutical composition, more preferably no more than about 15 weight percent, with the balance being pharmaceutically inert carrier(s).

The active compound is effective over a wide dosage range and is generally administered in a pharmaceutically effective amount. It, will be understood, however, that the amount of the compound actually administered will be determined by a physician, in the light of the relevant circumstances, including the condition to be treated, the chosen route of administration, the actual compound administered and its relative activity, the age, weight, and response of the individual patient, the severity of the patient's symptoms, and the like.

For preparing solid compositions such as tablets, the principal active ingredient is mixed with a pharmaceutical excipient to form a solid preformulation composition containing a homogeneous mixture of a compound of the present invention. When referring to these preformulation compositions as homogeneous, it is meant that the active ingredient is dispersed evenly throughout the composition so that the composition may be readily subdivided into equally effective unit dosage forms such as tablets, pills and capsules. This solid preformulation is then

subdivided into unit dosage forms of the type described above containing from, for example, 0.1 to about 500 mg of the active ingredient of the present invention.

The tablets or pills of the present invention may be coated or otherwise compounded to provide a dosage form affording the advantage of prolonged action. For example, the tablet or pill can comprise an inner dosage and an outer dosage component, the latter being in the form of an envelope over the former. The two components can be separated by an enteric layer which serves to resist disintegration in the stomach and permit the inner component to pass intact into the duodenum or to be delayed in release. A variety of materials can be used for such enteric layers or coatings, such materials including a number of polymeric acids and mixtures of polymeric acids with such materials as shellac, cetyl alcohol, and cellulose acetate.

The liquid forms in which the novel compositions of the present invention may be incorporated for administration orally or by injection include aqueous solutions, suitably flavored syrups, aqueous or oil suspensions, and flavored emulsions with edible oils such as corn oil, cottonseed oil, sesame oil, coconut oil, or peanut oil, as well as elixirs and similar pharmaceutical vehicles.

Compositions for inhalation or insufflation include solutions and suspensions in pharmaceutically acceptable, aqueous or organic solvents, or mixtures thereof, and powders. The liquid or solid compositions may contain suitable pharmaceutically acceptable excipients as described *supra*. Preferably the compositions are administered by the oral or nasal respiratory route for local or systemic effect. Compositions in preferably pharmaceutically acceptable solvents may be nebulized by use of inert gases. Nebulized solutions may be inhaled directly from the nebulizing device or the nebulizing device may be attached to a face mask tent, or intermittent positive pressure breathing machine. Solution, suspension, or powder compositions may be administered, preferably orally or nasally, from devices which deliver the formulation in an appropriate manner.

EXAMPLES

The following preparations and examples are given to enable those skilled in the art to more clearly understand and to practice the present invention. They should not be considered as limiting the scope of the invention, but merely as being illustrative and representative thereof.

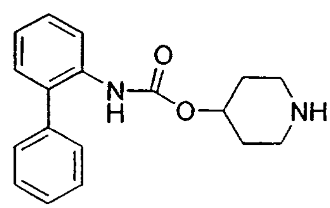
In the examples below, the following abbreviations have the following meanings. Unless otherwise stated, all temperatures are in degrees Celsius. If an abbreviation is not defined, it has its generally accepted meaning.

g	=	gram
mg	=	milligram
min	=	minute
ml	=	milliliter
mmol	=	millimol

Synthetic Examples

Example 1

Synthesis of 4-piperidyl-N-(2-biphenylyl)carbamate



Step 1

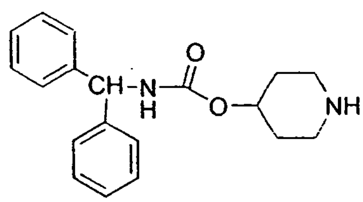
In a 50 ml sealed tube was added 2-biphenylylisocyanate (8 g, 41 mmol) in 40 ml anhydrous acetonitrile. To this solution was added N-benzyl-4-piperidinol (9.8 g, 51.25 mmol) and the tube was partially immersed in a silicon oil bath and heated to 85 °C. After 16 h, the reaction mixture was cooled and concentrated in *vacuo* to give a 1-benzyl-4-piperidyl N-(2-biphenylyl)carbamate which was used in the next step without further purification.

Step 2

1-Benzyl-4-piperidyl N-(2-biphenylyl)carbamate (12.5 g, 32.3 mmol) was dissolved in anhydrous methanol (150 ml) and formic acid (25 ml, 660 mmol) and the solution was flushed with gaseous nitrogen for 15 min. 10% Palladium on carbon (3 g) was added and the reaction mixture was stirred under nitrogen atmosphere . After 18 h, the reaction mixture was filtered through Celite[R] and the filtrate was concentrated to give a yellow solid. The solid was partitioned between 0.1 N hydrochloric acid (300 ml) and diethyl ethr (300 ml). The aqueous layer was washed with diethyl ether and then basified with 1 N sodium hydroxide solution to pH 12. A white solid precipitated out which was extracted into ethyl acetate. The ethyl acetate layer was dried over magnesium sulfate and evaporated to dryness to give 4-piperidyl N-(2-biphenylyl)carbamate as a colorless solid (6.63 g, 69%). MS= 296.9 MH+.

Example 2

Synthesis of 4-piperidyl benzhydrylcarbamate



Step 1

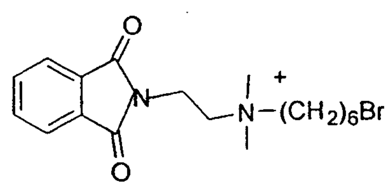
1-Benzyl-4-piperidinol (2.09 g, 10.9 mmol) and 4-nitrophenyl chloroformate (2.2 g, 10.9 mmol) were dissolved in anhydrous acetonitrile (10 ml). To this solution was added diisopropylethylamine (1.4 g, 10.9 mmol) and the resulting yellow solution was stirred at room temperature. After 3 h, aminodiphenylmethane (2 g, 10.9 mmol) was added and the reaction mixture was heated at 65 °C. After 3 h, the reaction mixture was cooled to room temperature and stirred for an additional 12 h. The resulting solid was filtered, washed with cold acetonitrile to give 1-benzyl-4-piperidyl benzhydrylcarbamate (1.3 g, 50%) as a colorless solid which was used in the next step without further purification.

Step 2

1-benzyl-4-piperidyl benzhydrylcarbamate (1.1 g, 4.5 mmol) was dissolved in anhydrous methanol (15 ml) and formic acid (5 ml, 132 mmol) and the solution was flushed with gaseous nitrogen for 15 min. 10% Palladium on carbon (0.3 g) was added and the reaction mixture was stirred under nitrogen atmosphere . After 18 h, the reaction mixture was filtered through Celite[R] and the filtrate was concentrated to give a yellow solid. The solid was partitioned between 0.1 N hydrochloric acid (300 ml) and diethyl ether (300 ml). The aqueous layer was washed with diethyl ether and then basified with 1 N sodium hydroxide solution to pH 12. A white solid precipitated out which was extracted into ethyl acetate. The ethyl acetate layer was dried over magnesium sulfate and evaporated to dryness to give 4-piperidyl benzhydrylcarbamate (108) as a colorless solid (0.65 g, 78%). MS= 311.3 MH+.

Example 3

Synthesis of N-[N-(3,3-dimethyl)-N-(6-bromohexyl)aminopropyl)phthalimide quaternary ammonium salt



Step 1

N-(3-bromopropyl)phthalimide (10 g, 37.3 mmol) was dissolved in dry acetonitrile (100 ml) and a solution of dimethylamine in tetrahydrofuran (56 ml, 111 mmol, 2 M) was added. The flask was fitted with a reflux condense and the solution was heated at reflux. After 22 h, the reaction mixture was concentrated in vacuo to give a yellow oil which was partitioned between ethyl acetate and 1 M sodium carbonate solution saturated with sodium chloride. The organic phase was collected and washed with brine, dried over potassium carbonate, filtered and concentrated to give a yellow oil. The oil was dissolved in methanol (25 ml) and p-

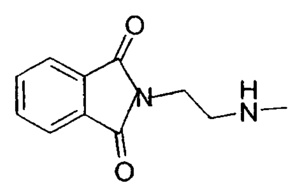
toluenesulfonic acid (7.80 g, 41 mmol) was added. The solution was diluted with ether to crystallize the N-(3,3-dimethylaminopropyl)phthalimide as the p-toluenesulfonic acid salt (8.0 g). MS (M-OTs)$^+$ 233.1.

Step 2

p-Toluenesulfonic acid salt of N-(3-dimethylaminopropyl)phthalimide (0.42 g, 0.98 mmol) was partitioned between ethyl acetate and 1 M sodium carbonate. The aqueous phase was separated, saturated with sodium chloride and then extracted with ethyl acetate. The organic layers were washed with water and brine, dried over potassium carbonate, filtered and concentrated in vacuo to give an oil. The oil was dissolved in dry acetonitrile (10 ml) and 1,6-dibromohexane (1.21 g, 4.90 mmol) was added. The reaction mixture was cooled to room temperature and diluted with one volume of ether. The resulting solids were filtered to give N-[N-(3,3-dimethyl)-N-(6-bromohexyl)aminopropyl)phthalimide quaternary ammonium salt as a white solid. MS 395.2 (M-Br)+.

Example 4

Synthesis of N-(2-methylaminoethyl)phthalimido

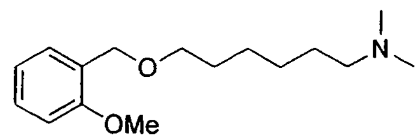


Step 1

N-Methylethylenediamine (3.38 g, 45.6 mmol) was dissolved in chloroform (60 ml) and a solution of N-carbethoxyphthalimide (10 g, 45.6 mmol) in chloroform (30 ml) was added rapidly. After 6 h, the clear solution was concentrated in vacuo to give an iol which was dissolved in methanol, acidifed with 4 M hydrochloric acid in dioxane (15 ml). Diethyl ether was added to crystallize N-(2-methylaminoethyl)-phthalimido as the chloride salt (9.25 g, 84%). MS 205 (M-Cl)+.

Example 5

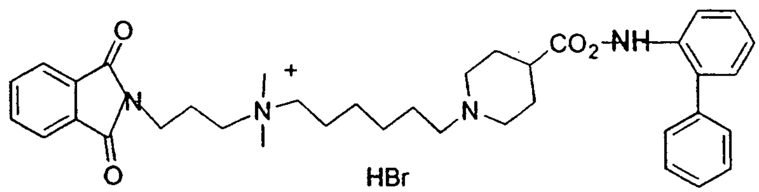
Synthesis of *O*-(2-methoxybenzyl)-6-dimethylaminohexanol



6-(Dimethylamino)hexanol (8.80 g, 60.6 mmol) was dissolved in an anhydrous 2:1 mixture of tetrahydrofuran and dimethylformamide (150 ml) and the solution was cooled in an ice bath. Sodium hydride (60% in oil, 3.23 g, 80.8 mmol) was added in portions and after 5 min. the water bath was removed. After 45 min., 2-methoxybenzyl chloride (6.28 g, 40.4 mmol) was added. After 4 h, the reaction mixture was quenched with 1 M sodium thiosulfate and tetrahydrofuran was removed in *vacuo*. The reaction mixture was washed with ethyl acetate and the aqueous phase was basified with 3 m sodium hydroxide, followed by extraction with ether. The ether layer was dried over potassium carbonate, filtered and acidified with 4 M hydrochloric acid in dioxane. The reaction mixture was concentrated in *vacuo* and the residue was crystallized form ethanol/ether to give *O*-(2-methoxybenzyl)-6-dimethylaminohexanol as the hydrochloride salt (10.4 g, 85%). MS (M-Cl)+ 266.3.

Example 6

Synthesis of 1-N-[N-(3,3-dimethylaminopropyl)phthalimid0)-6-[4-piperidyl-N-(2-biphenylyl)carbamate hydrobromide salt

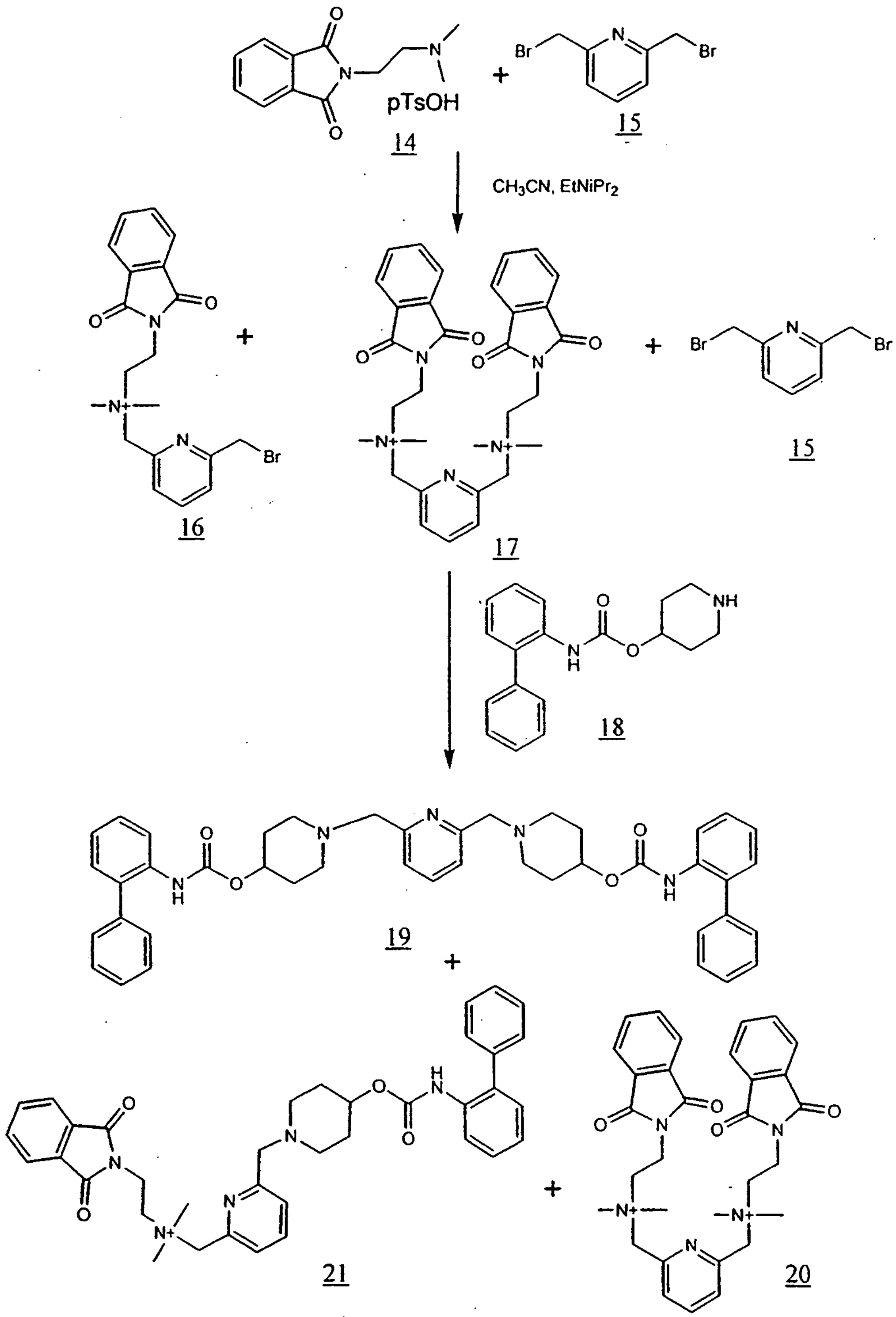


To N-[N-(3,3-dimethyl)-N-(6-bromohexyl)aminopropyl)phthalimide quaternary ammonium salt (16 mg, 0.03 mmol) , prepared as above, in acetonitrile

(1 ml) was added 4-piperidyl N-(2-biphenylyl)carbamate (10 mg, 0.03 mmol), prepared as above, and the reaction mixture was heated at reflux for 3 h. The reaction mixture was cooled to room temperature, and the product precipitated as the hydrobromide salt. The solids were isolated by filtration to give 20 mg (77%) of the desired product as white solids. The product was characterized by NMR (MeOH) and MS (calculated, $(M\text{-}HBr_2)^+ = 611.3600$; found, 611.5).

Example 7

Synthesis of compounds of Formula (I) via combinatorial chemistry


pTsOH
14
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CH3CN, EtNiPr2
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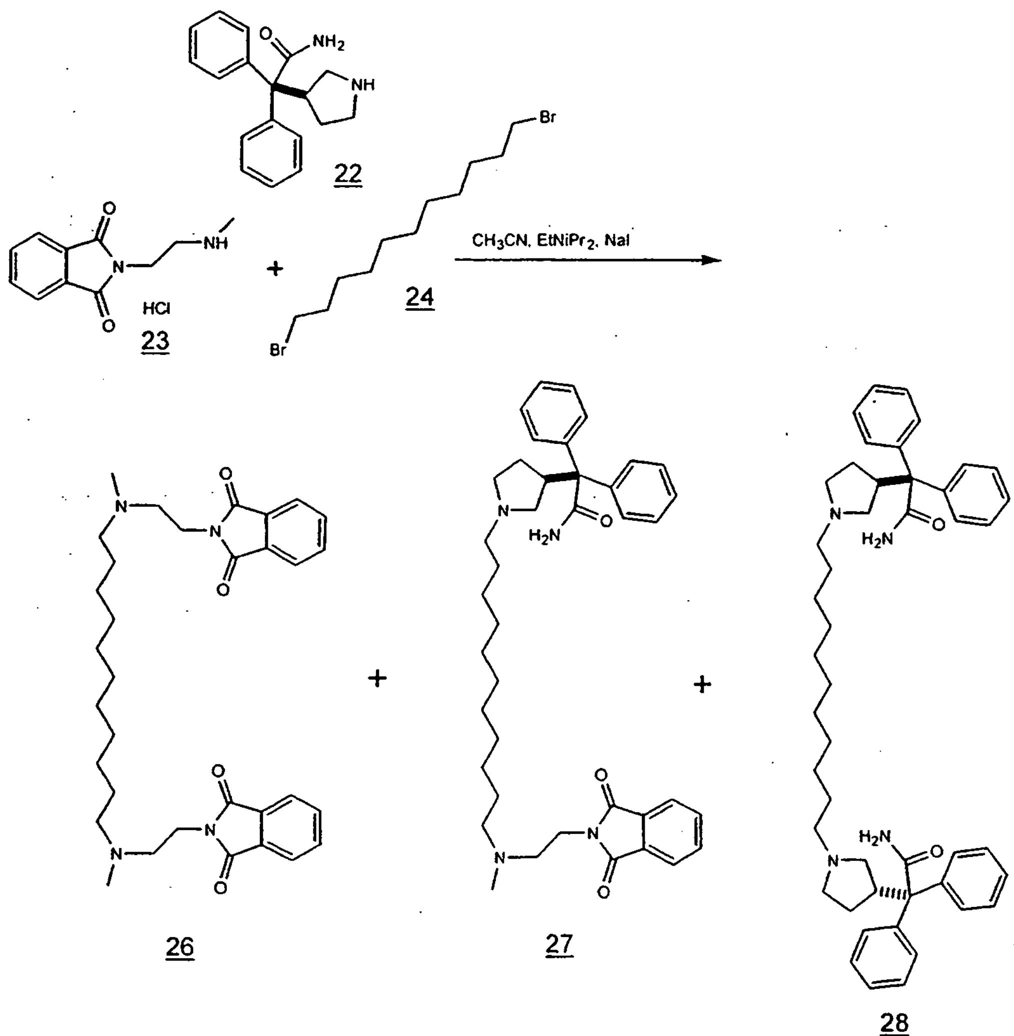
An aliquot (0.22 mL) of a solution prepared from N-[2-dimethylamino)-ethyl]phthalimido 14 (1.25 g, 3.2 mmol) and $EtNiPr_2$ (0.79 mL) dissolved in enough anhydrous acetonitrile to bring the total volume up 6.4 mL was added to a 1 dram vial charged with 2,6-bis(bromomethyl)pyridine (Aldrich, 26.5 mg, 0.10 mmol) in 0.22 mL of acetonitrile). The vial was closed with a Teflon sealed cap and the placed in a 72 °C heating block for a 24 h to give a mixture of compounds 15, 16, and 17. After cooling to room temperature, 4-piperidyl-N-(2-biphenyl)-carbamate 18 (0.33 mL) (prepared by dissolving 2.96 g of 18 in anhydrous DMF to produce a total volume of 33 mL) was added and the vial is resealed and heated overnight at 72 °C in a heating block. The mixture was cooled, quenched with 5% TFA/water (0.30 mL), diluted with acetonitrile and water, filtered, and purified using preperative LC/MS [Zeng, L; Kassel, D. B. *Anal. Chem.* **1998**, *70*, 4380-4388 and references therein] to provide the individual components. Quality and identity of the collected fractions was verified using analytical HPLC and electrospray MS.

Example 8

Synthesis of compounds of Formula (I) via combinatorial chemistry



N-(2-Methylaminethyl)phthalimido 23 (0.20 mL, of a 0.5 M solution, 0.10 mmol) (prepared by dissolving 168 mg of N-(2-methylaminethyl)phthalimido in, DIPEA (0.18 mL) and enough anhydrous acetonitrile to bring the solution to a total volume of 1.4 mL), and a solution of compound 22 (0.167 mL) (prepared by dissolving 673 mg of 22 in enough anhydrous acetonitrile to bring the total volume to 4 mL), and NaI (0.20 mL of a 1 M solution in anhydrous acetonitrile) were combined in a 1 dram vial charged with 1,11-dibromoundecane (0.10 mmol). The

vial was closed with a Teflon sealed cap and the placed in a 72 °C heating block for a 21 h. The mixture was cooled, quenched with 5% TFA/water (0.30 mL), diluted with acetonitrile and water, filtered, and purified using preperative LC/MS [Zeng, L; Kassel, D. B. *Anal. Chem.* **1998**, *70*, 4380-4388 and references therein] to provide the individual components 26-28. Quality and identity of the collected fractions was verified using analytical HPLC and electrospray MS.

Following the procedures described above but substituting appropriate starting materials, compounds of Formula (I) listed in Table III below were prepared.

TABLE 3

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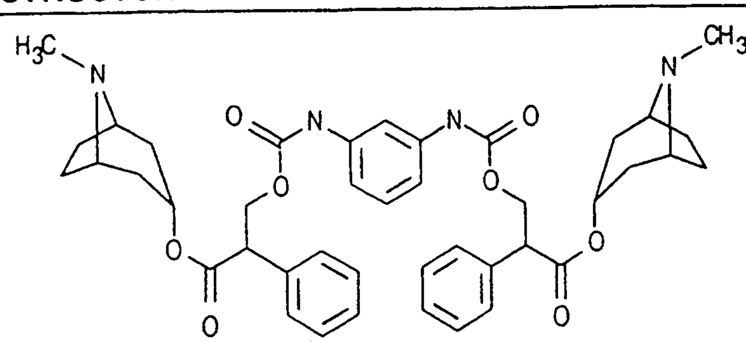
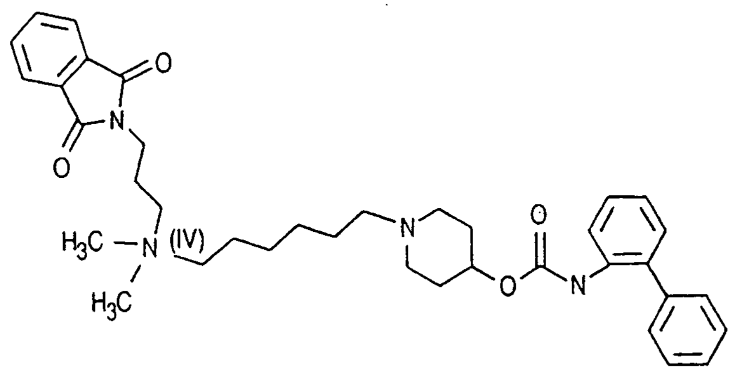
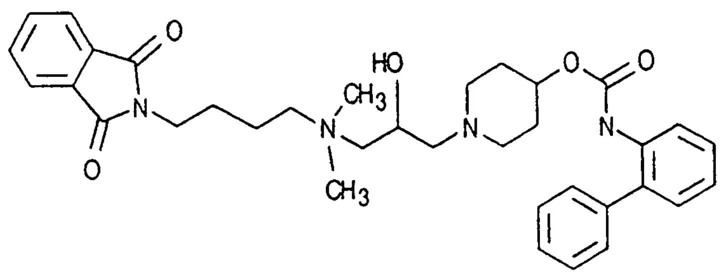
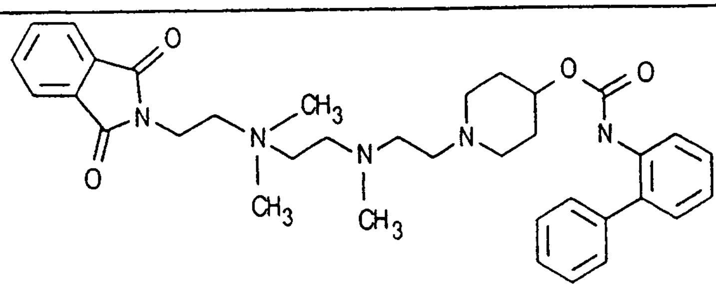
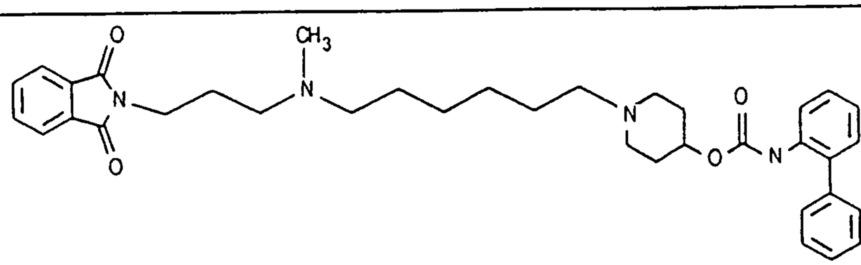
1	
2	
3	
4	
5	

TABLE 3

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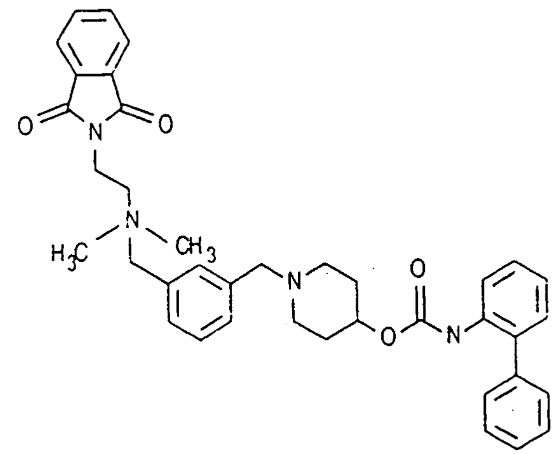
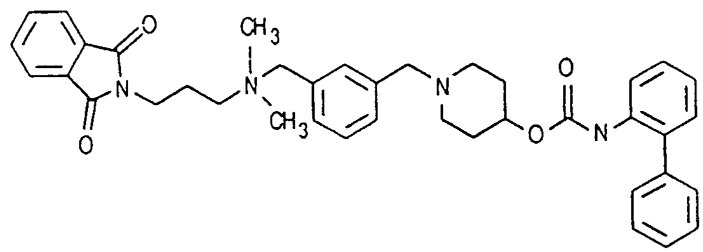
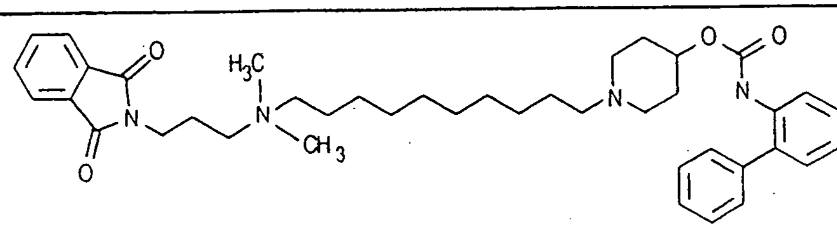
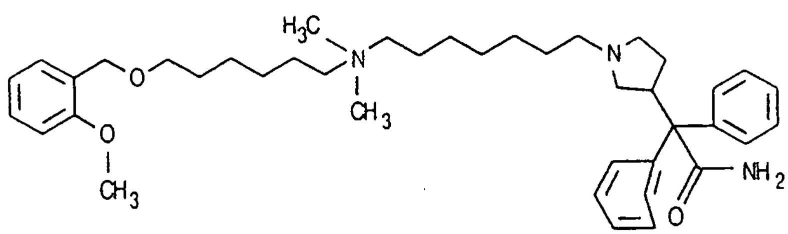
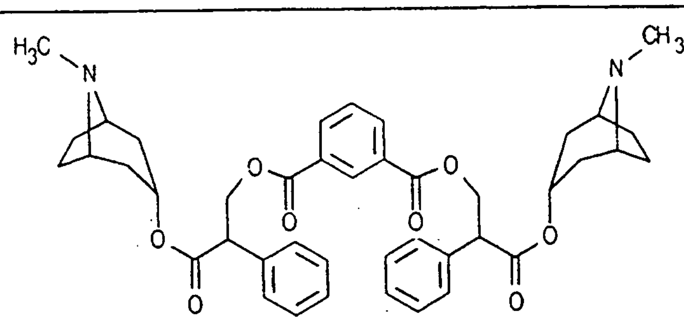
6	
7	
8	
9	
10	

TABLE 3

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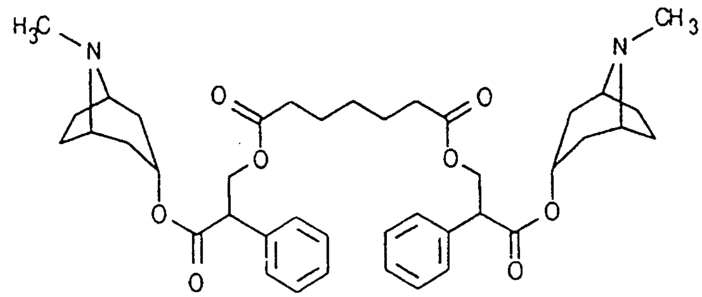
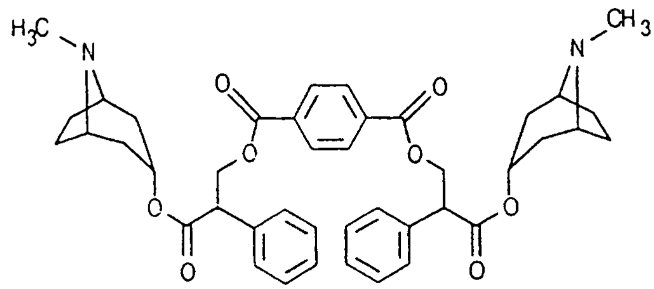
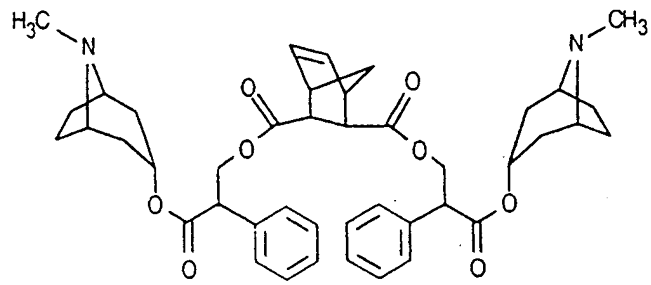
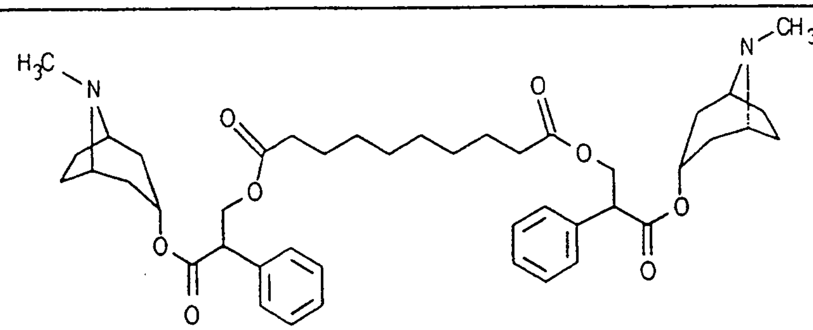
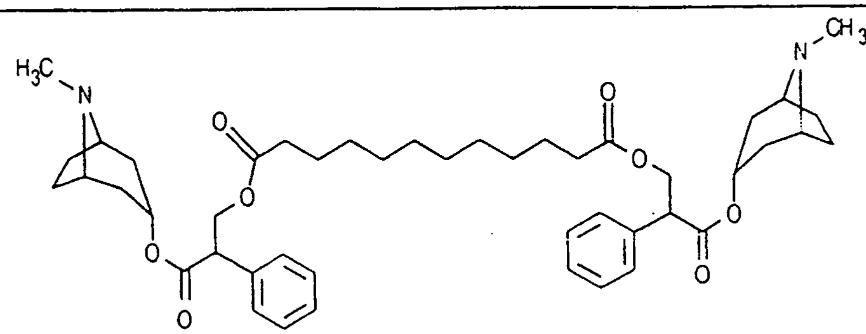
11	
12	
13	
14	
15	

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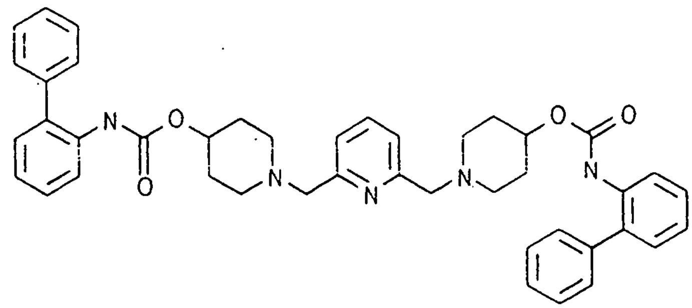
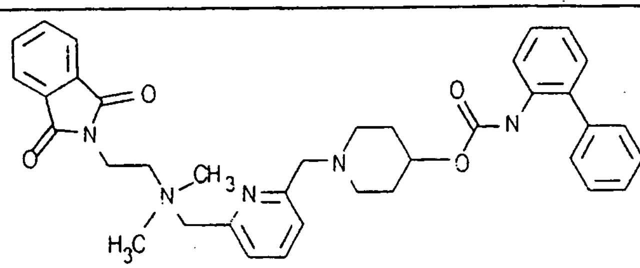
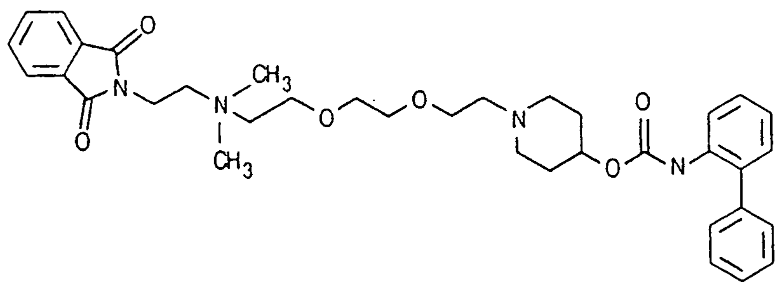
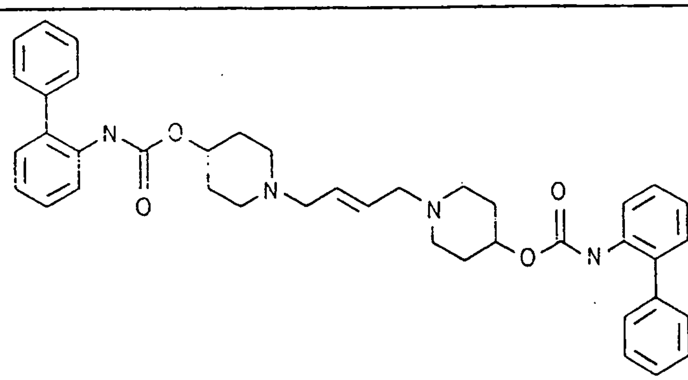
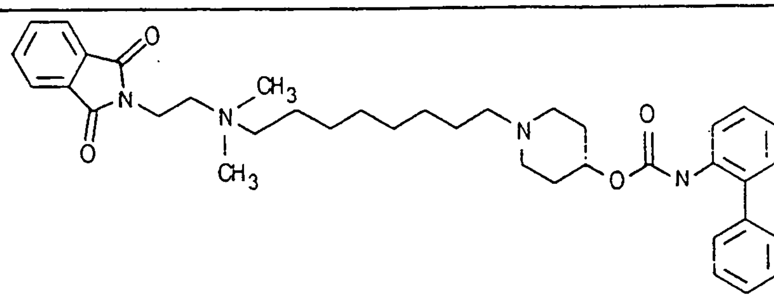
16	
17	
18	
19	
20	

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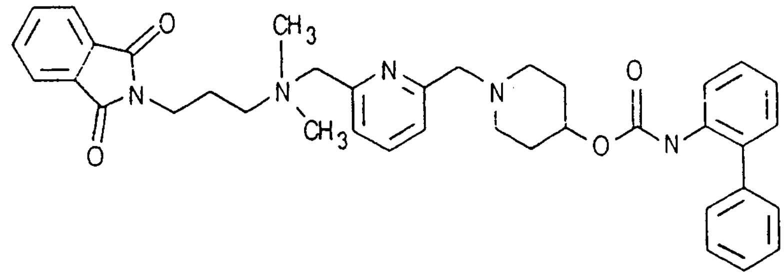
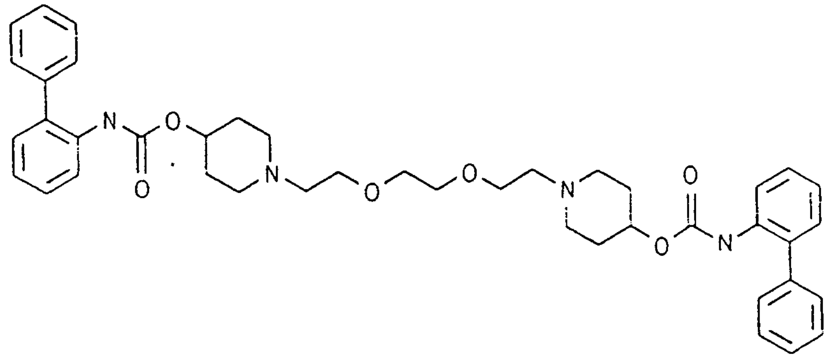
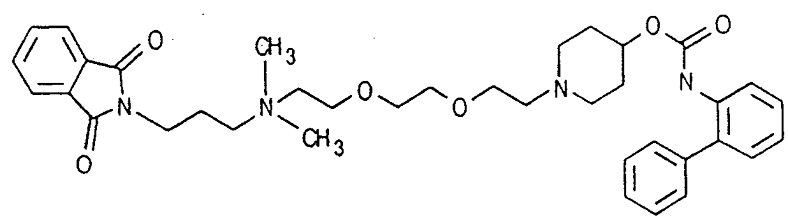
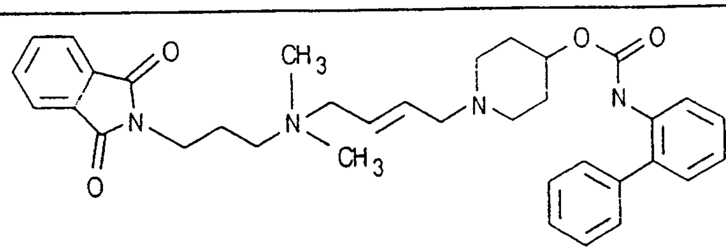
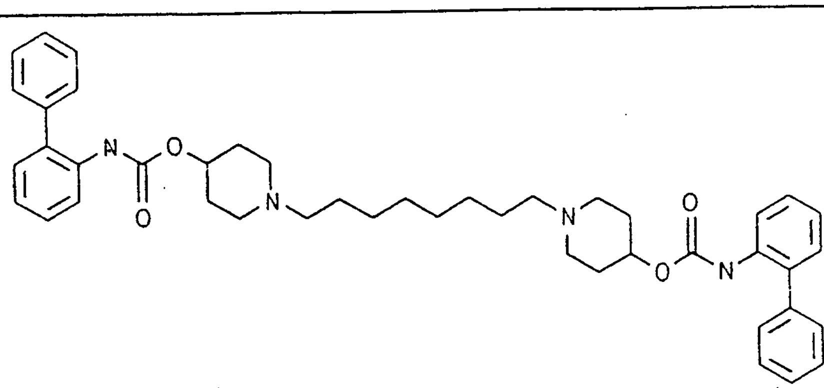
21	
22	
23	
24	
25	

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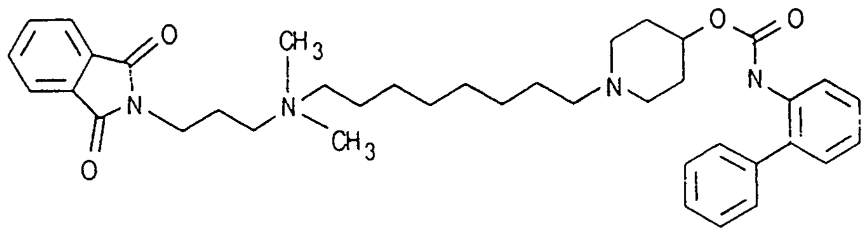
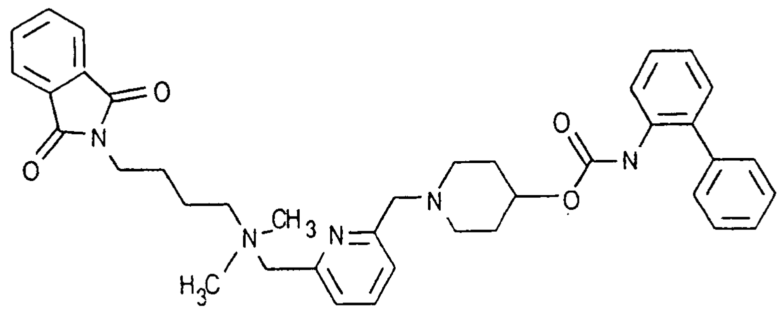
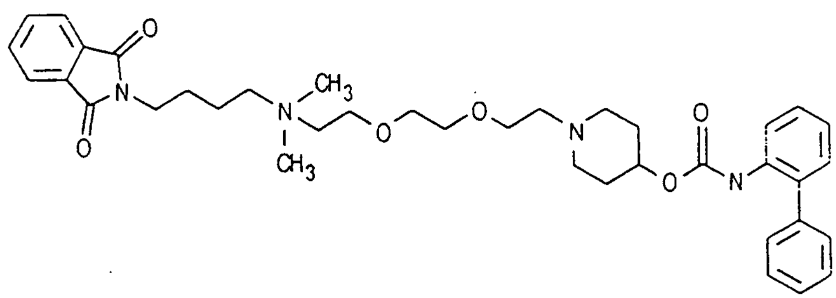
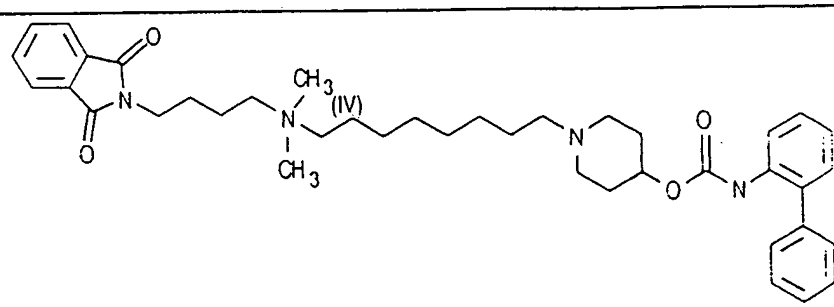
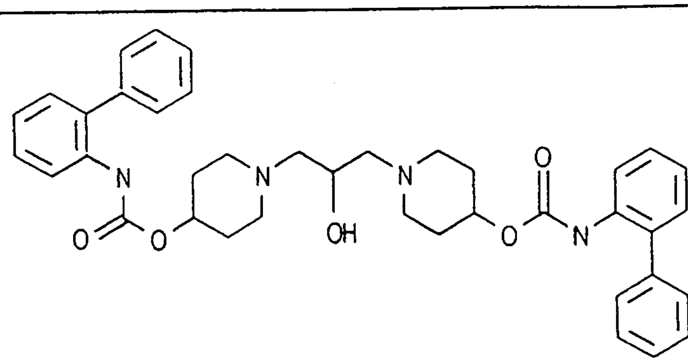
26	
27	
28	
29	
30	

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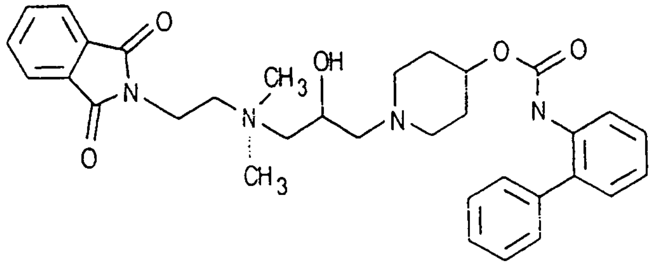
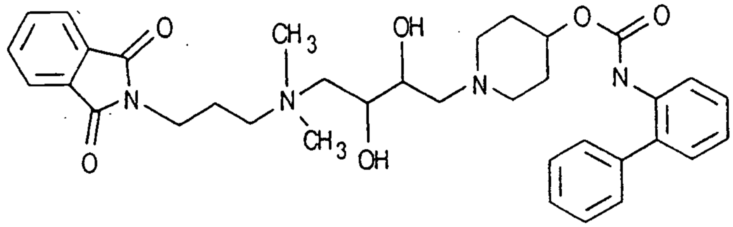
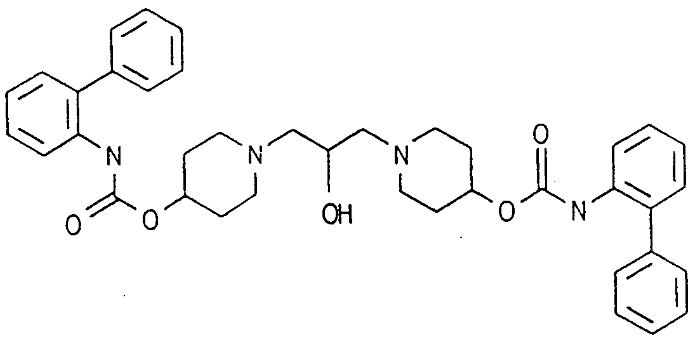
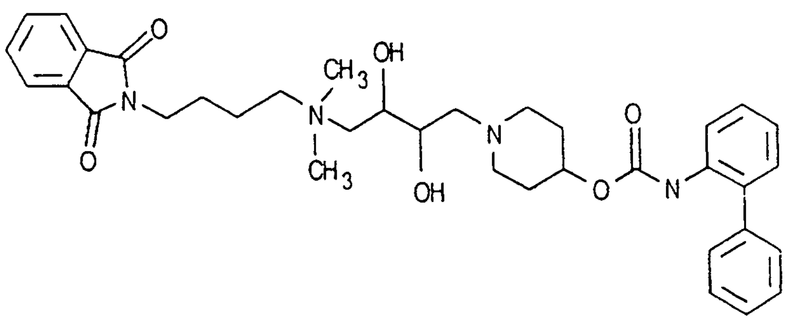
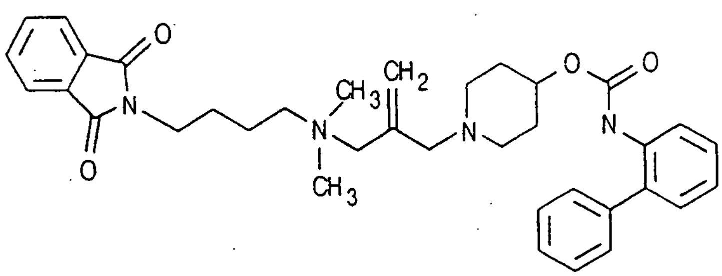
31	
32	
33	
34	
35	

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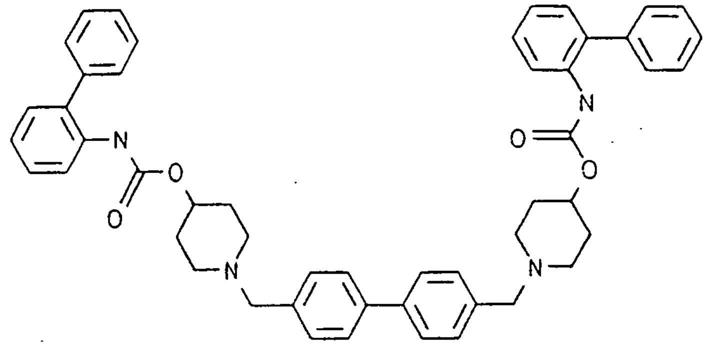
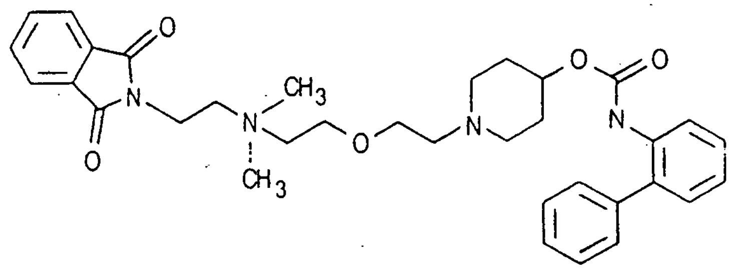
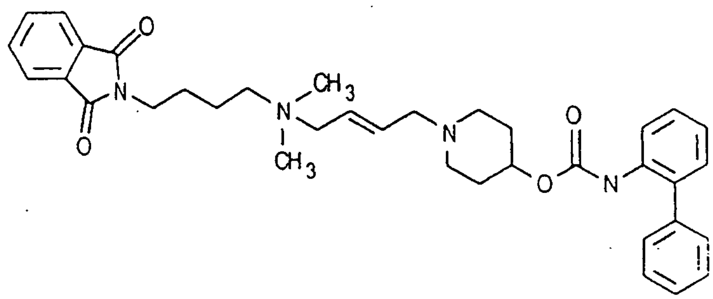
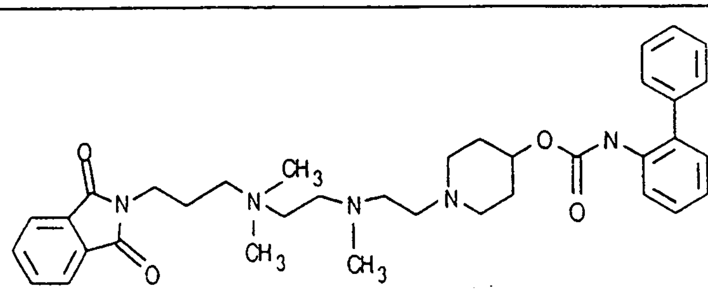
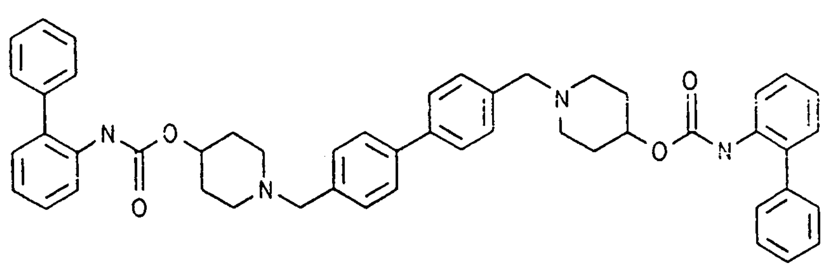
36	
37	
38	
39	
40	

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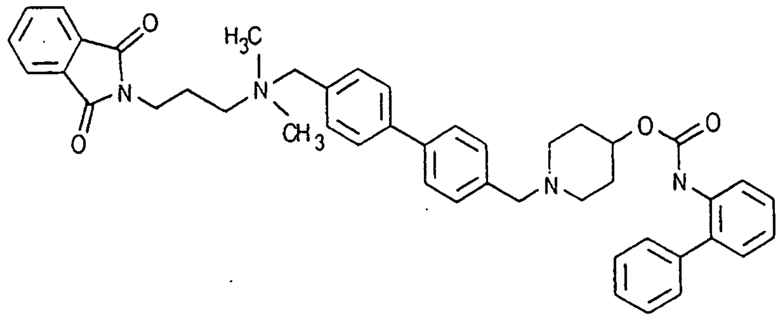
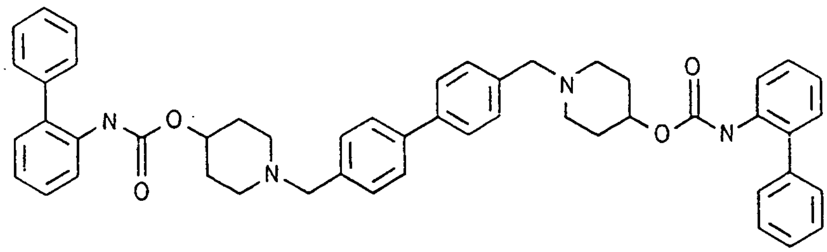
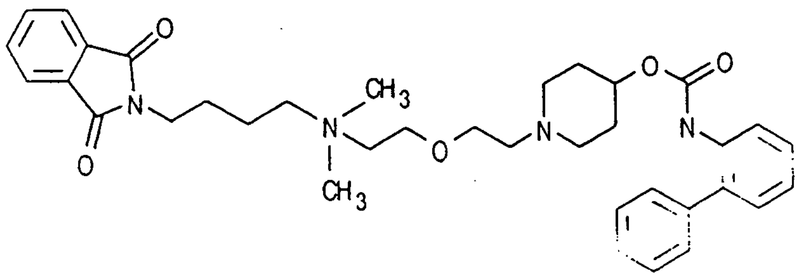
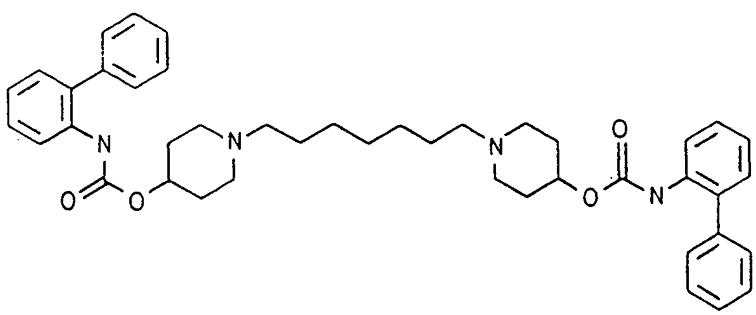
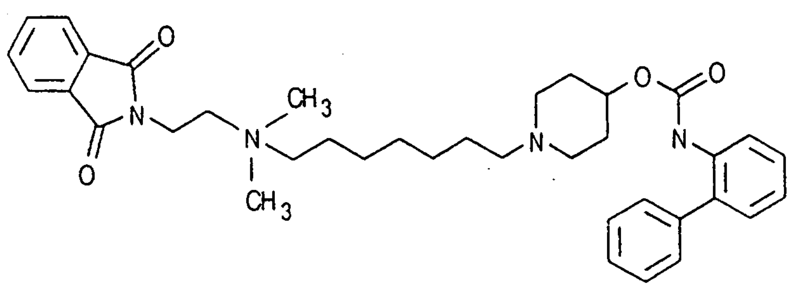
41	
42	
43	
44	
45	

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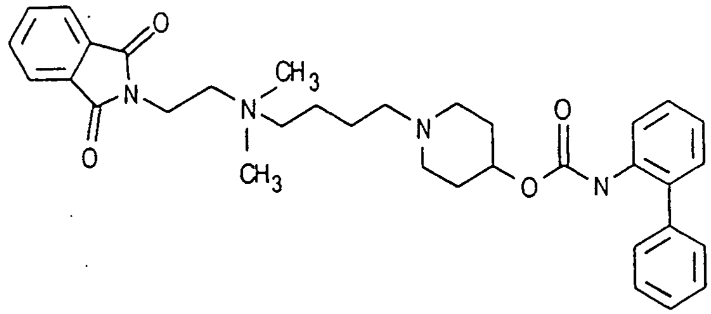
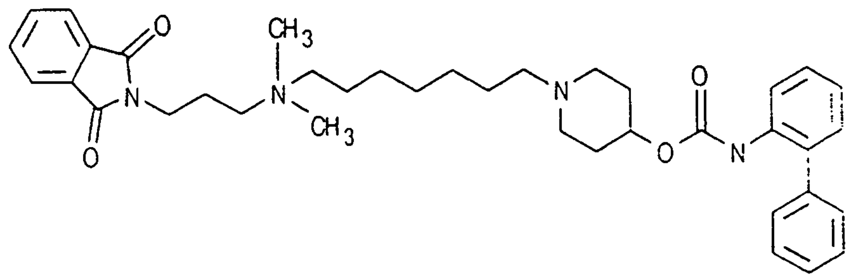
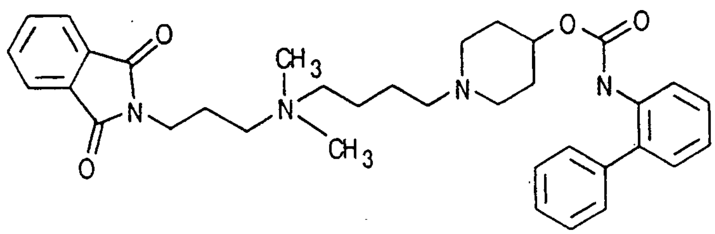
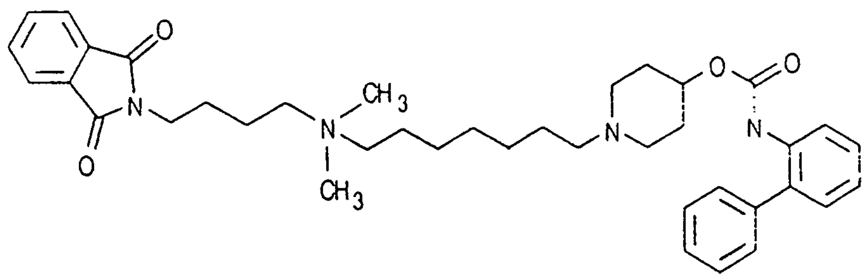
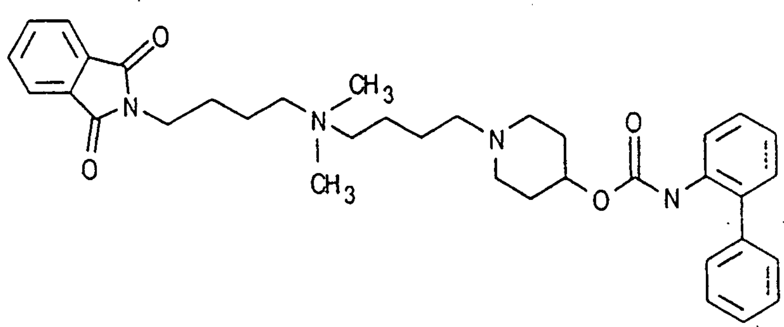
46	
47	
48	
49	
50	

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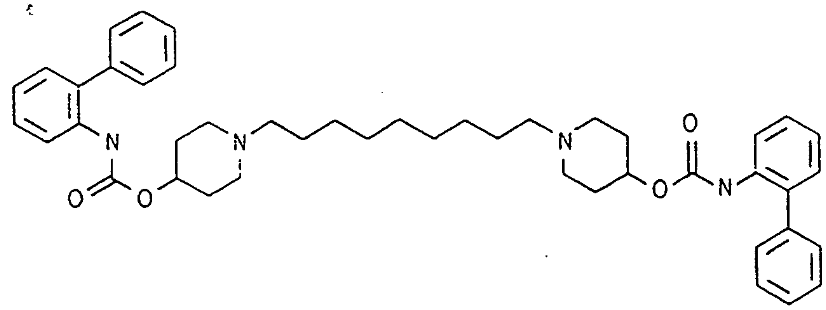
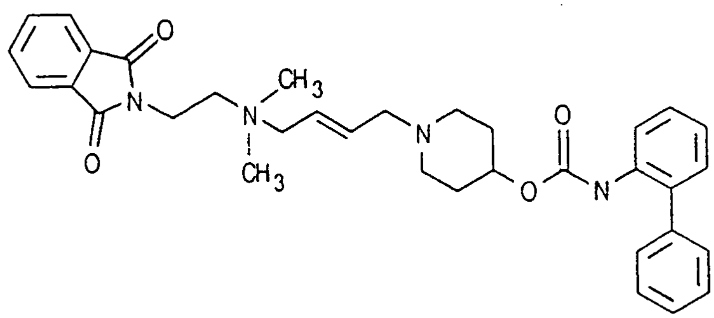
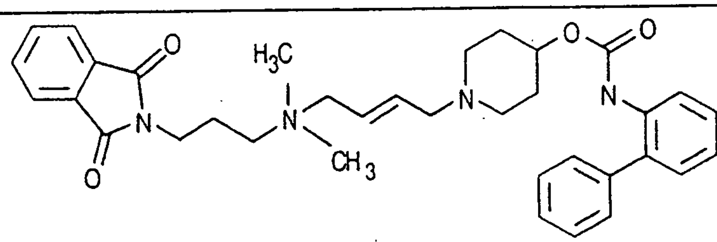
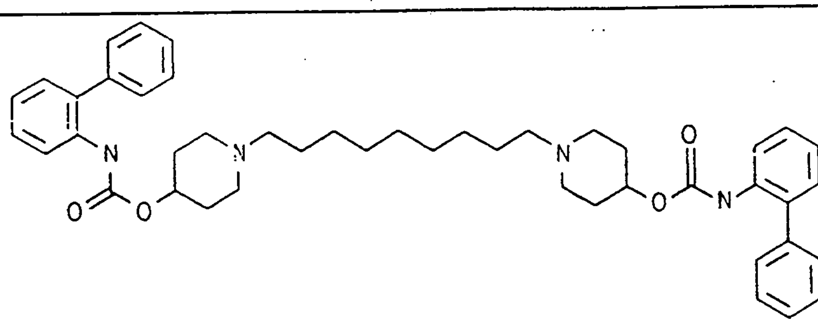
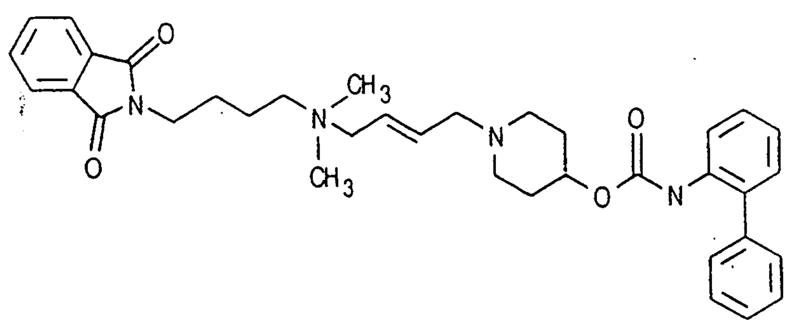
51	
52	
53	
54	
55	

TABLE 3

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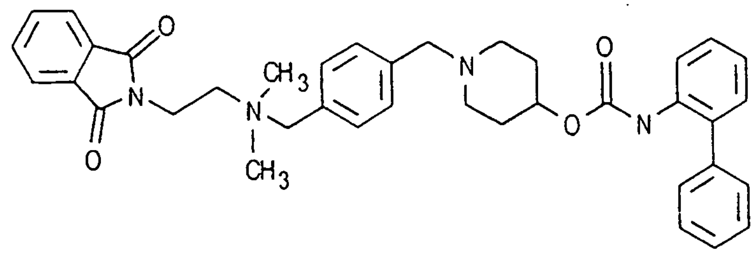
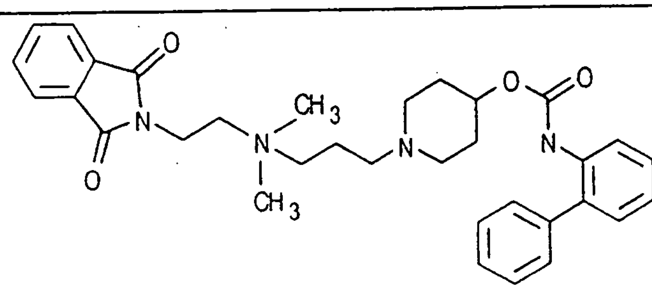
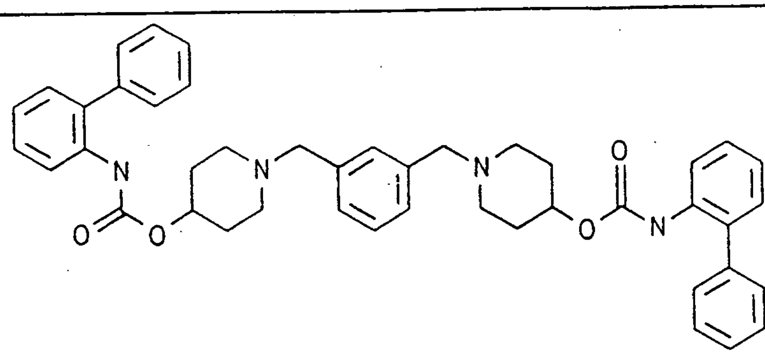
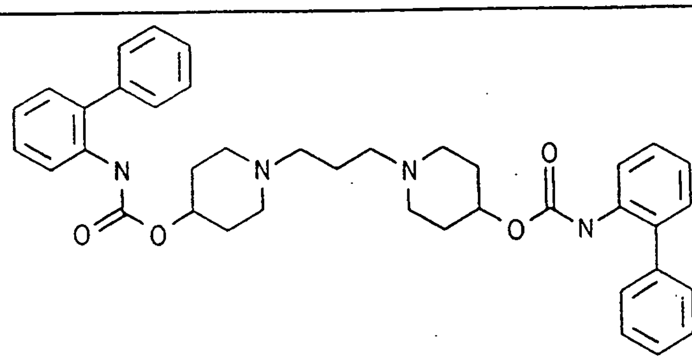
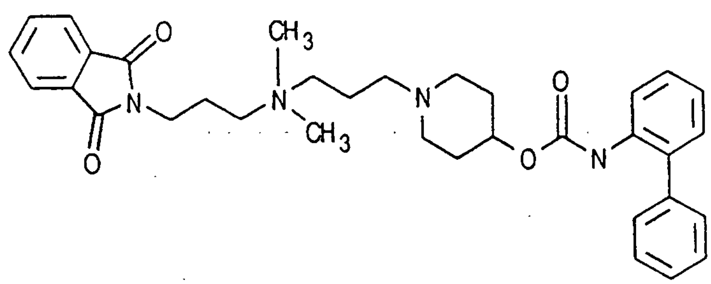
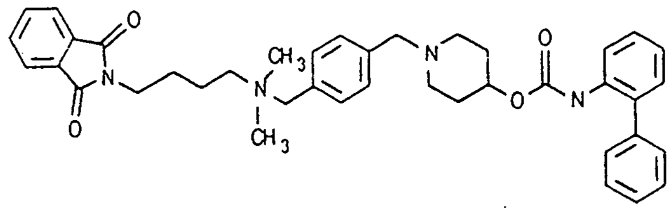
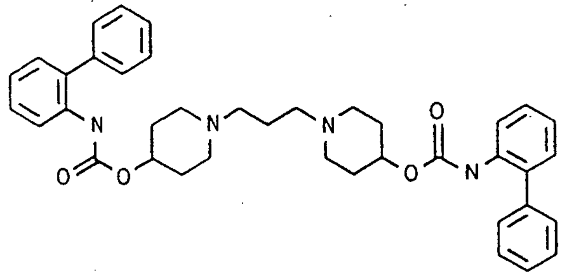
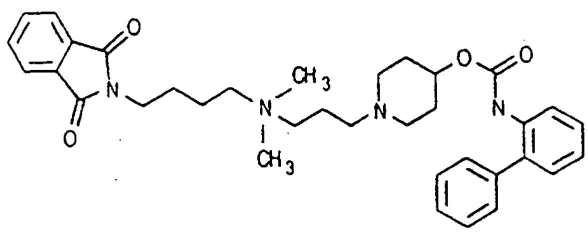
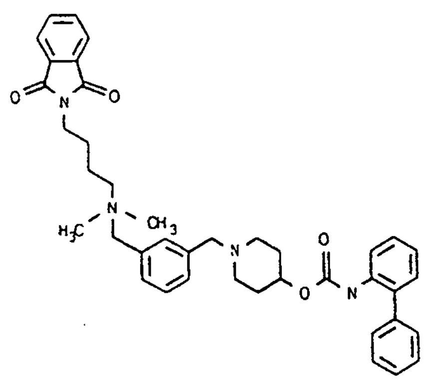
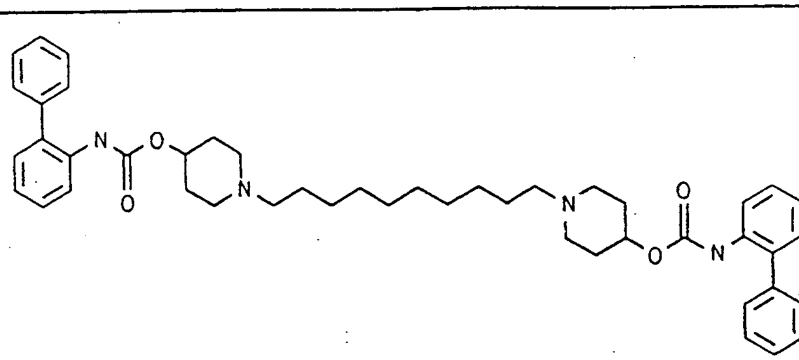
56	
57	
58	
59	
60	

TABLE 3

#	STRUCTURE
61	
62	
63	
64	
65	

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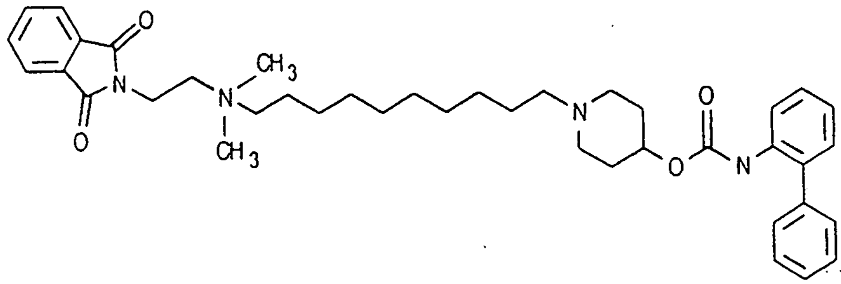
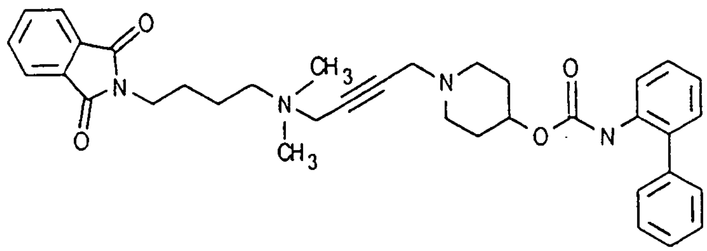
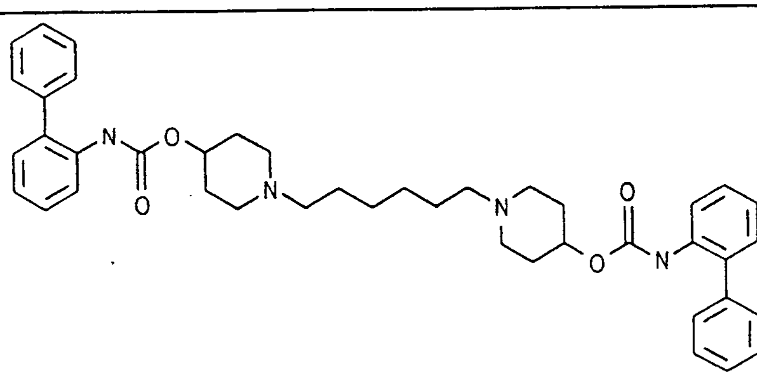
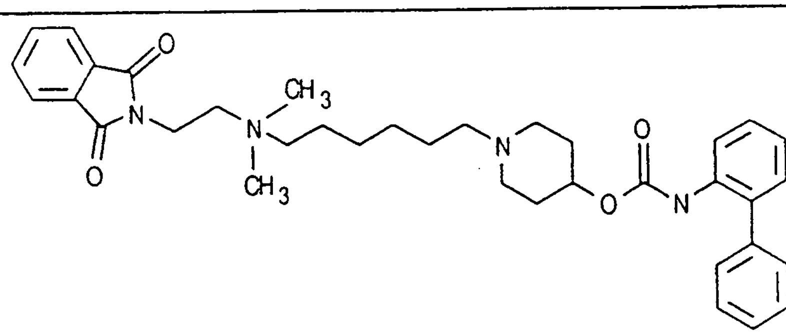
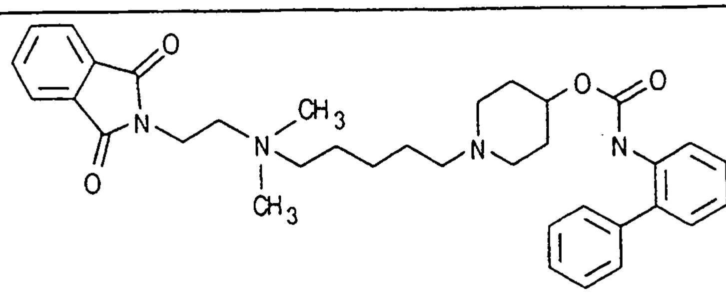
66	
67	
68	
69	
70	

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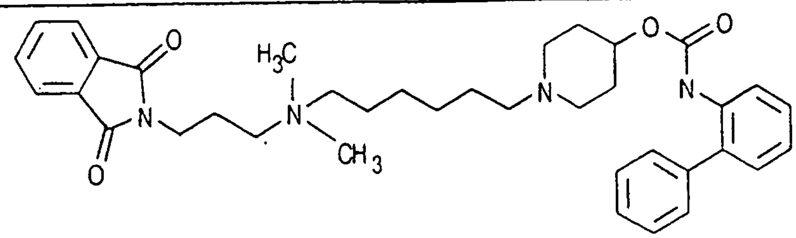
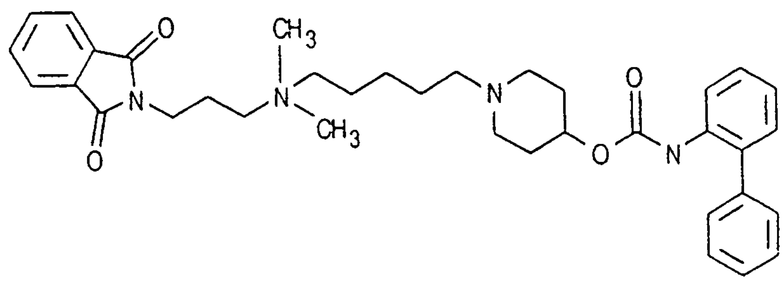
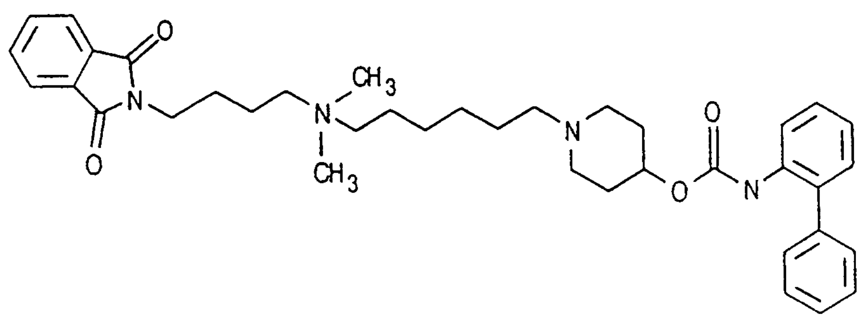
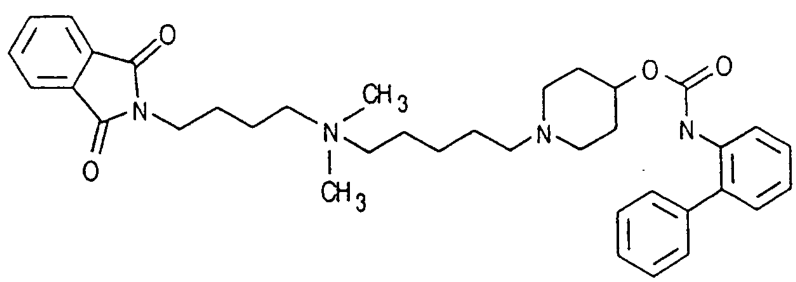
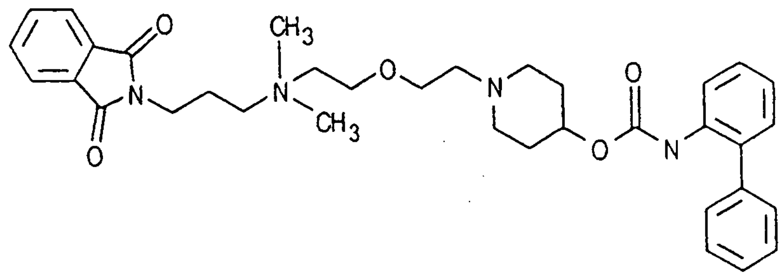
71	
72	
73	
74	
75	

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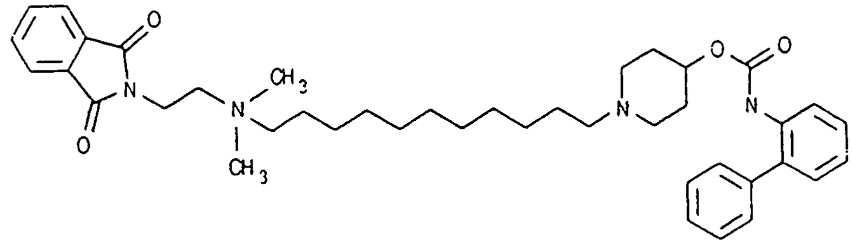
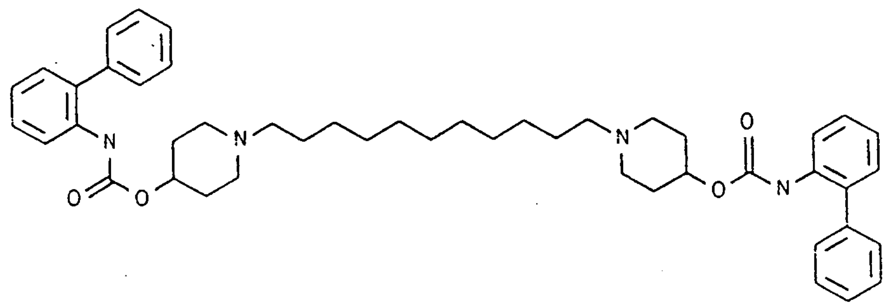
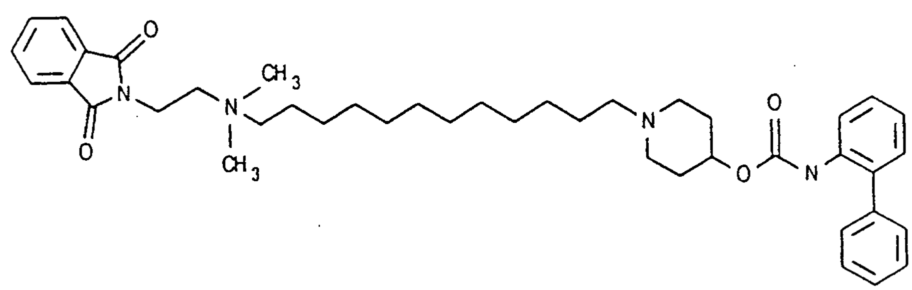
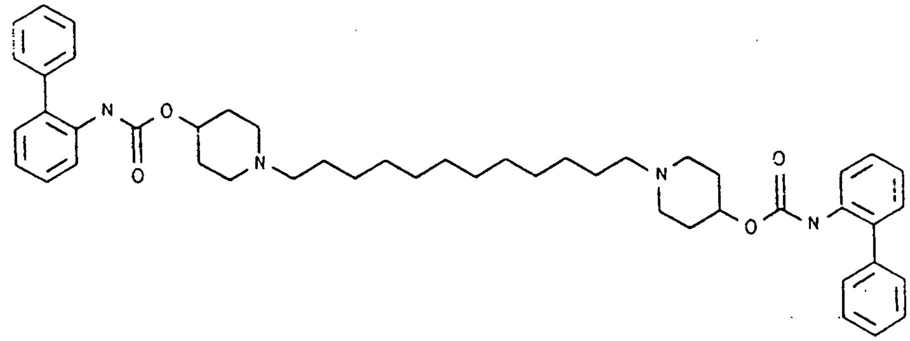
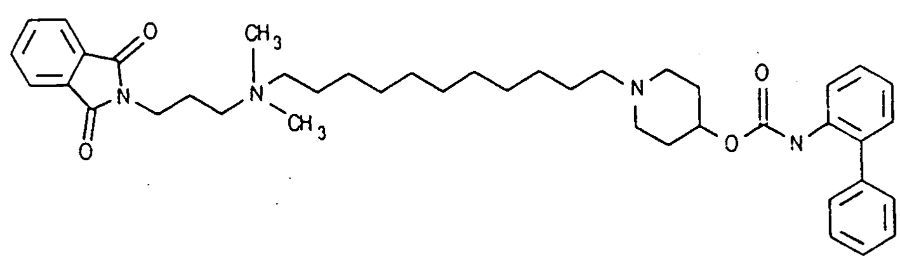
76	
77	
78	
79	
80	

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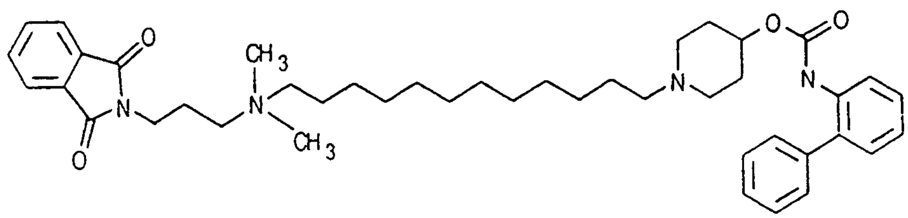
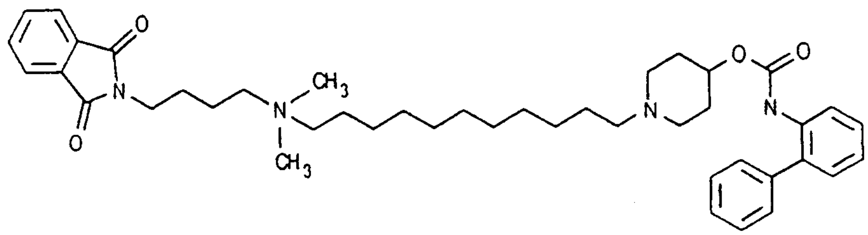
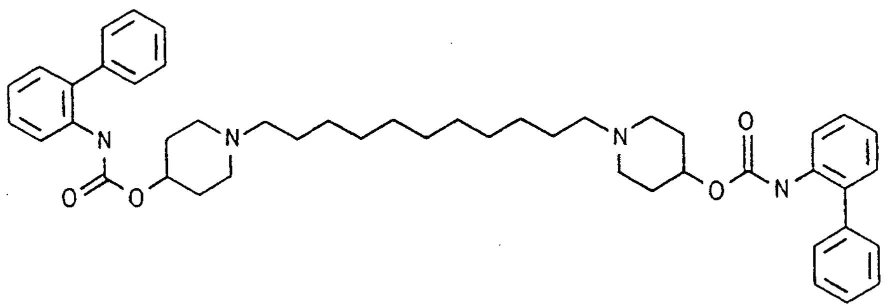
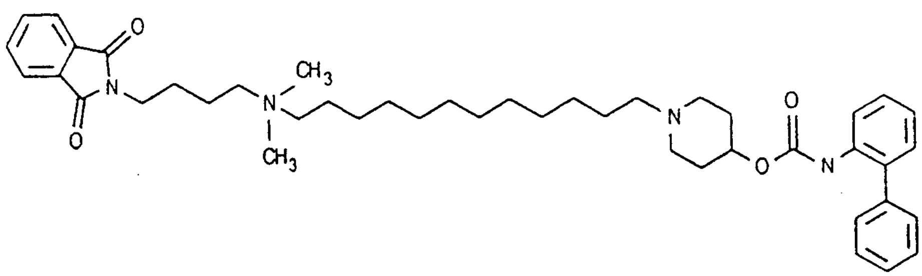
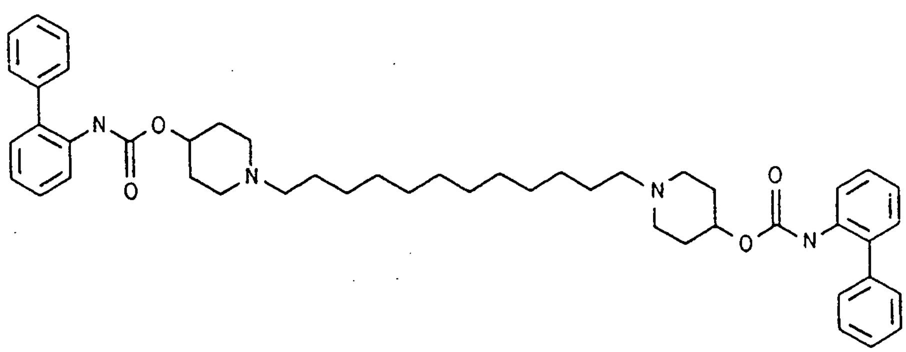
81	
82	
83	
84	
85	

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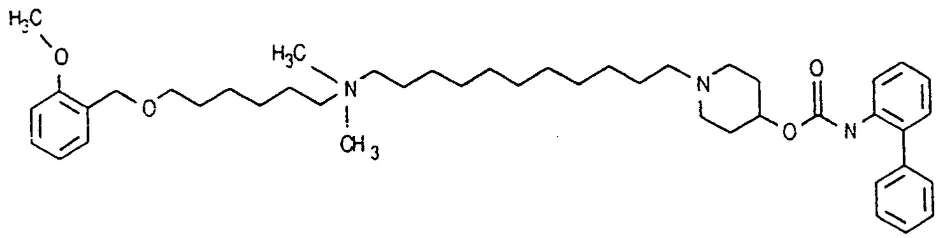
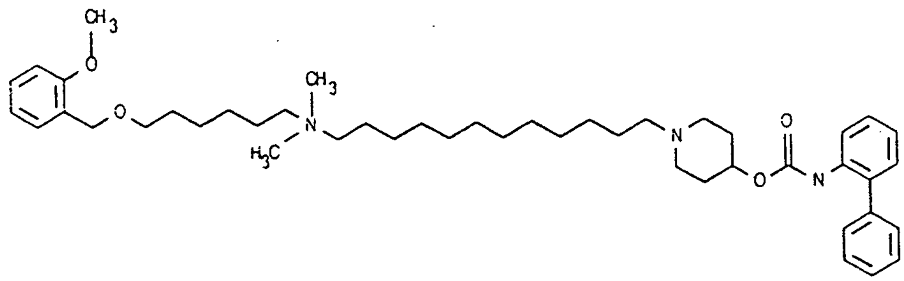
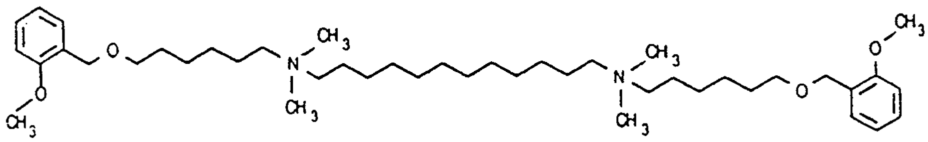
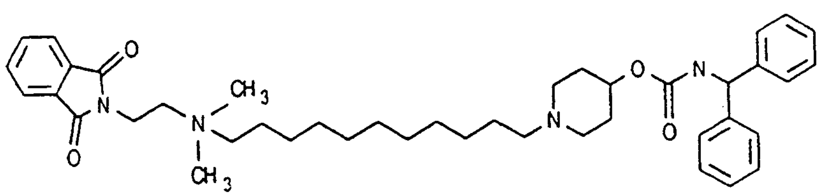
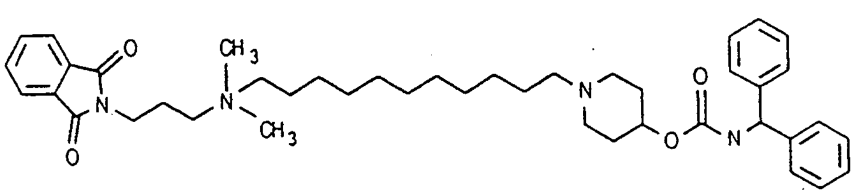
86	
87	
88	
89	
90	

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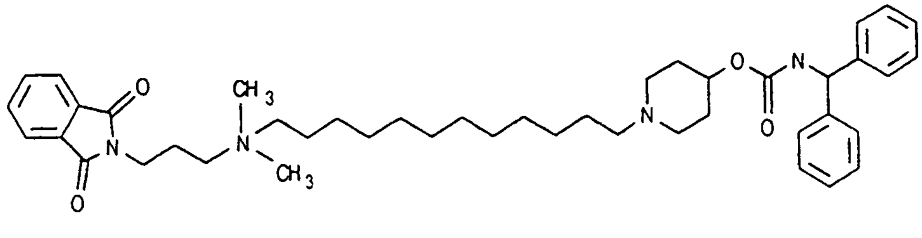
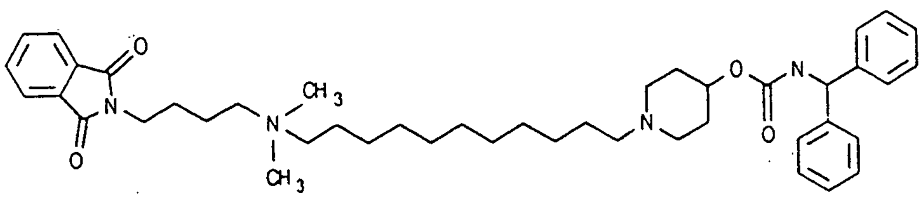
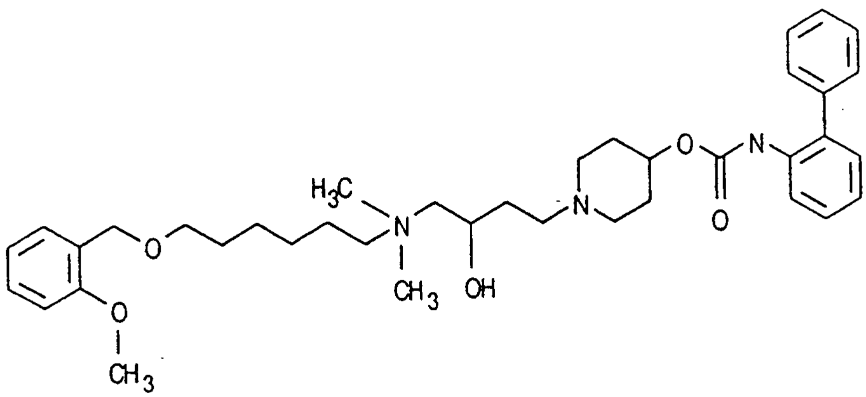
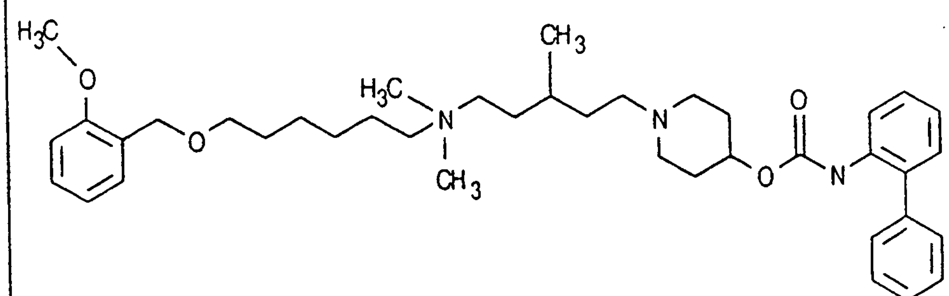
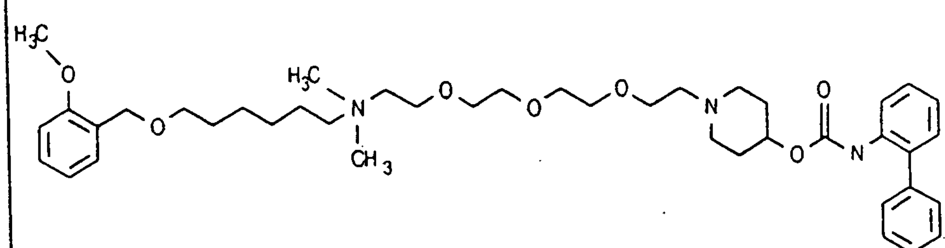
91	
92	
93	
94	
95	

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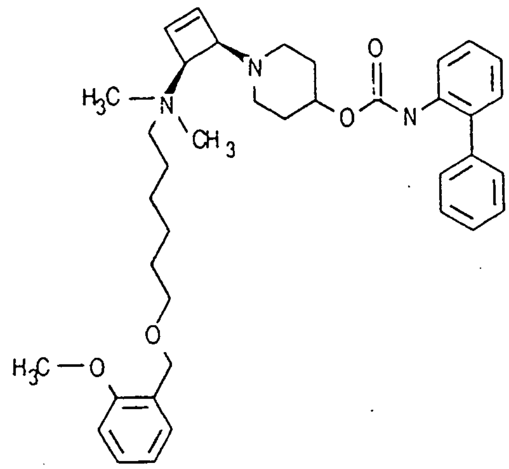
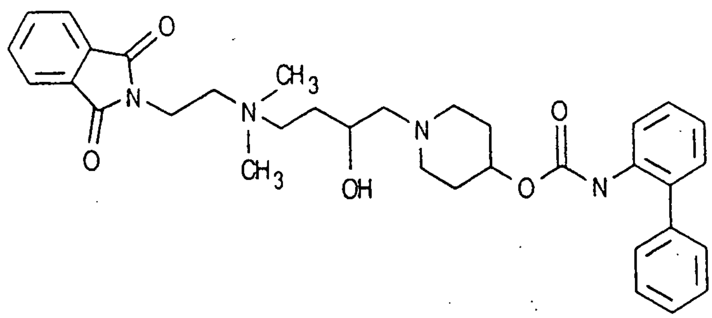
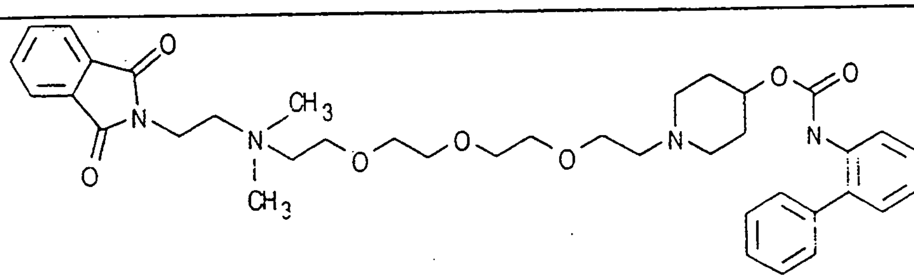
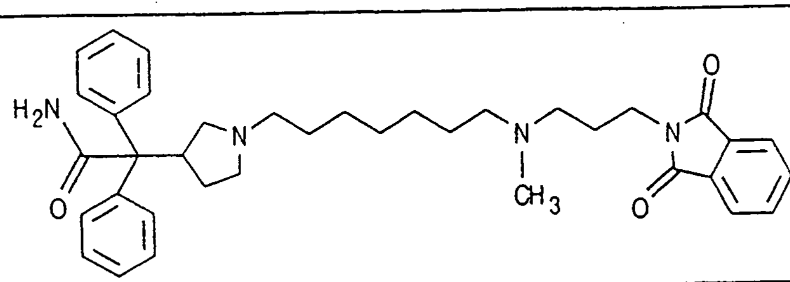
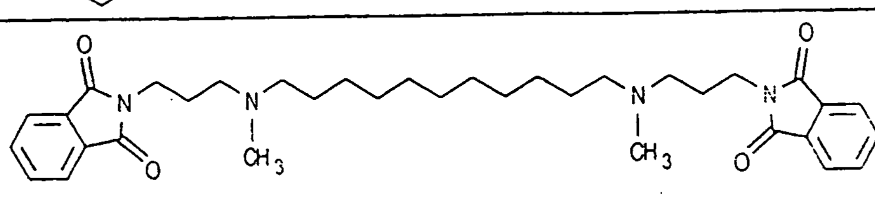
96	
97	
98	
99	
100	

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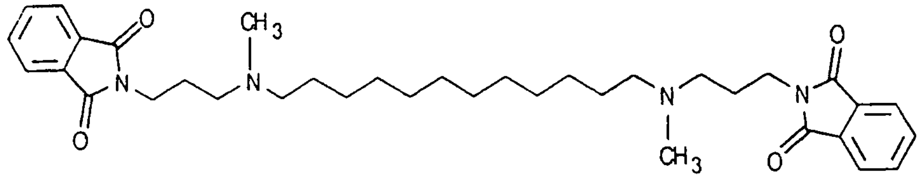
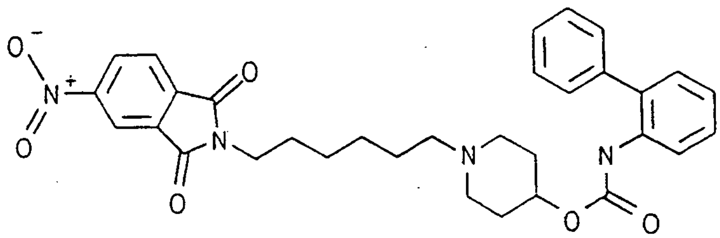
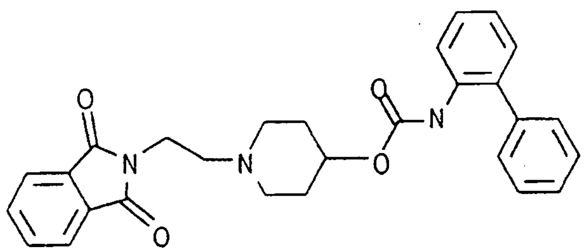
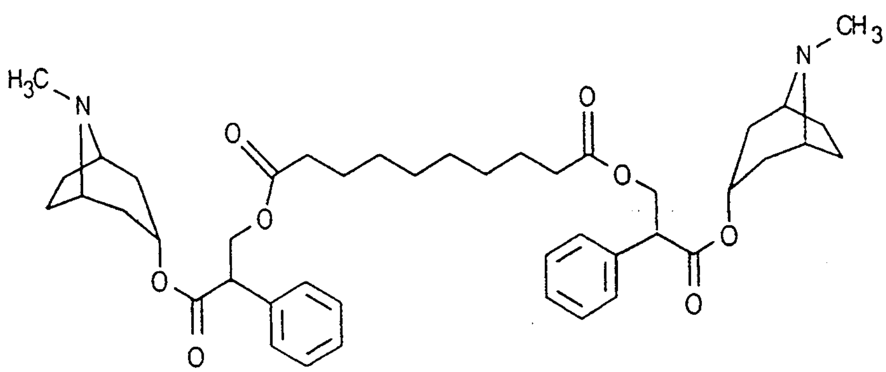
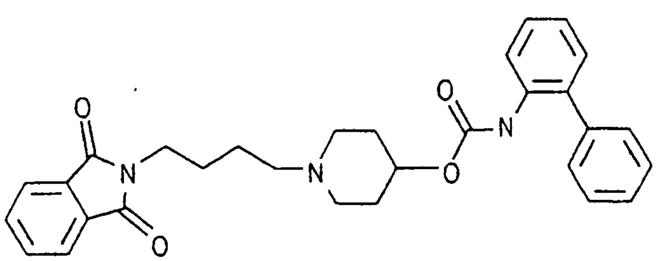
101	
102	
103	
104	
105	

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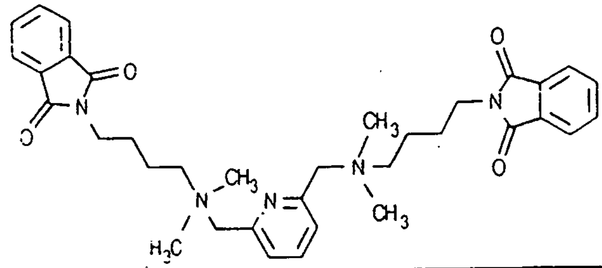
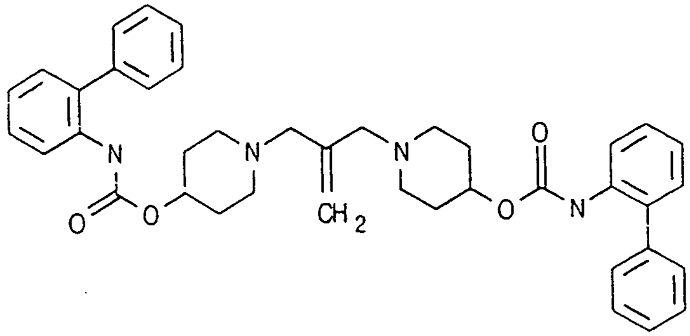
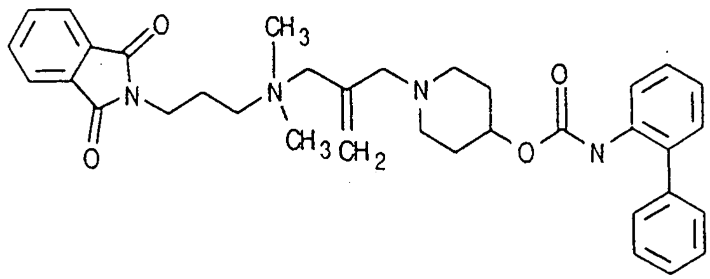
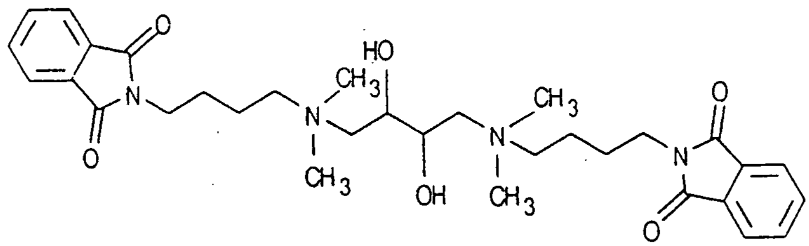
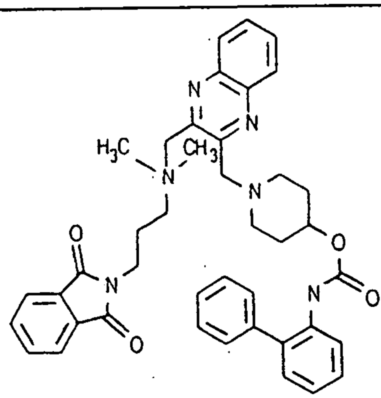
106	
107	
108	
109	
110	

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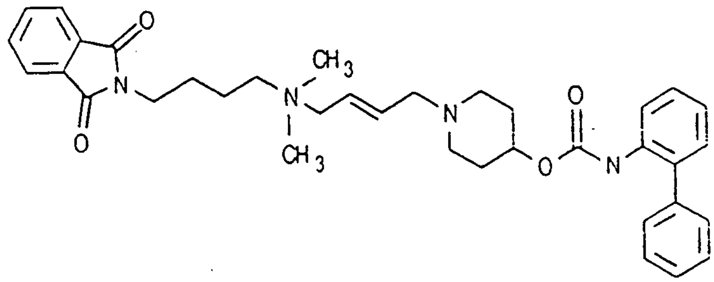
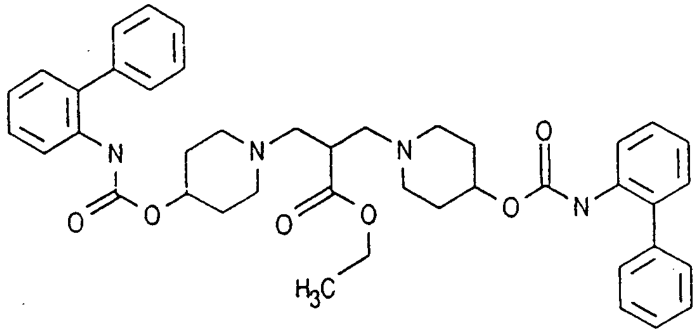
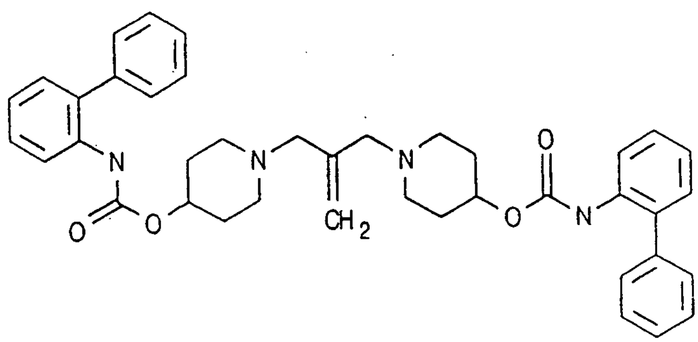
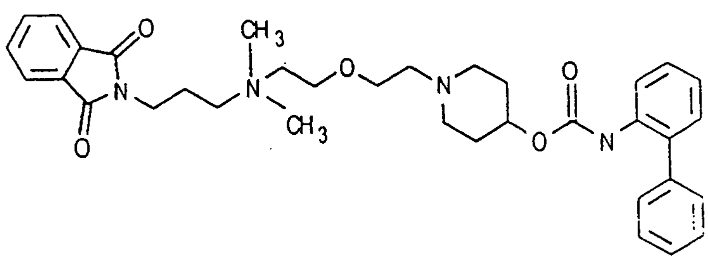
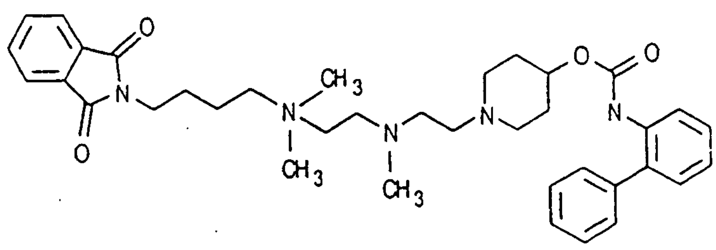
111	
112	
113	
114	
115	

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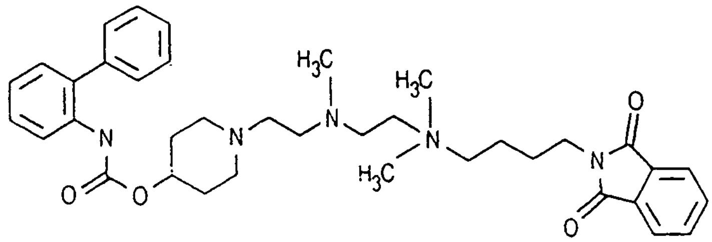
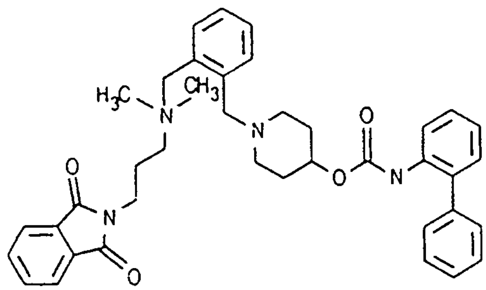
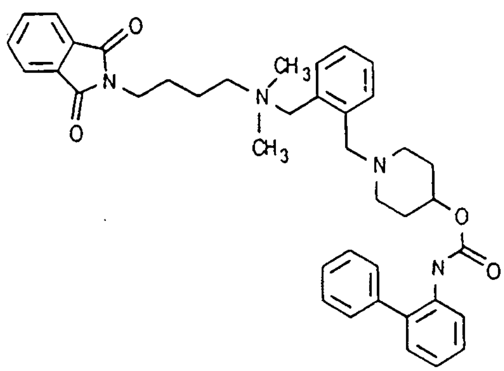
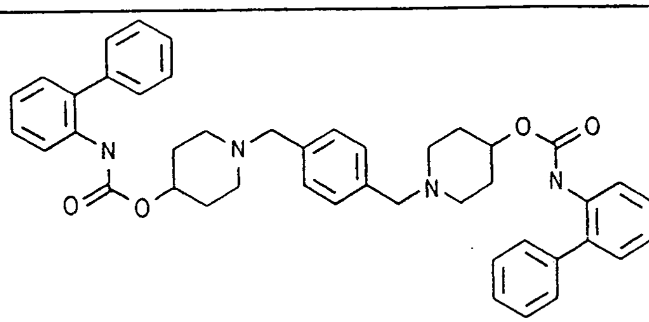
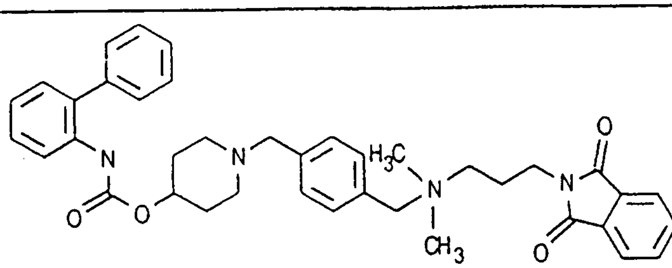
116	
117	
118	
119	
120	

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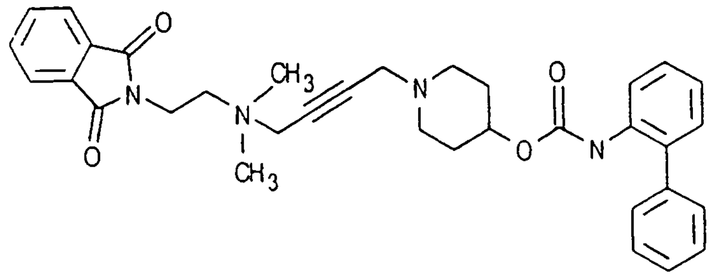
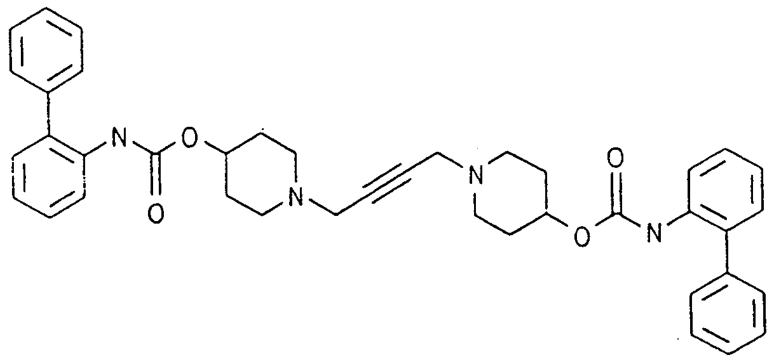
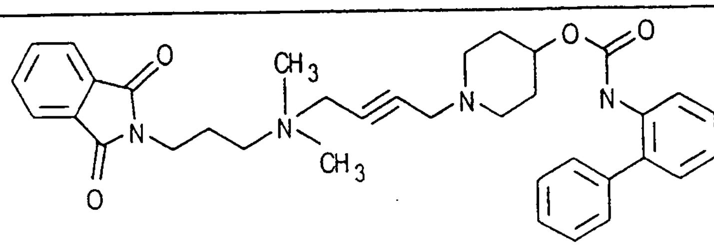
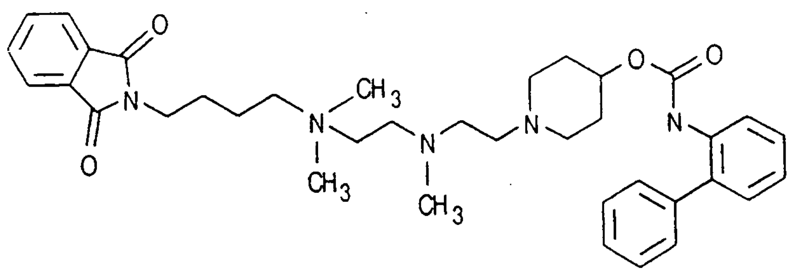
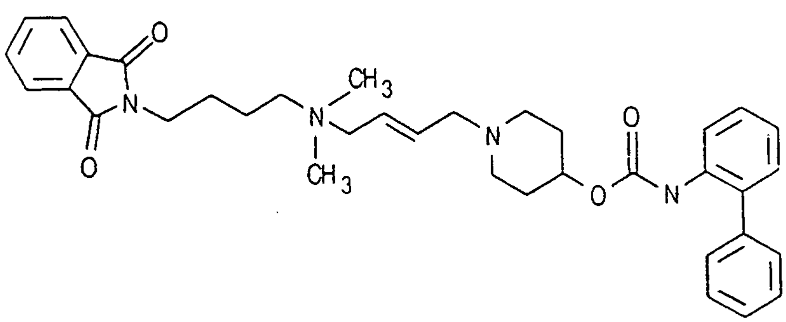
121	
122	
123	
124	
125	

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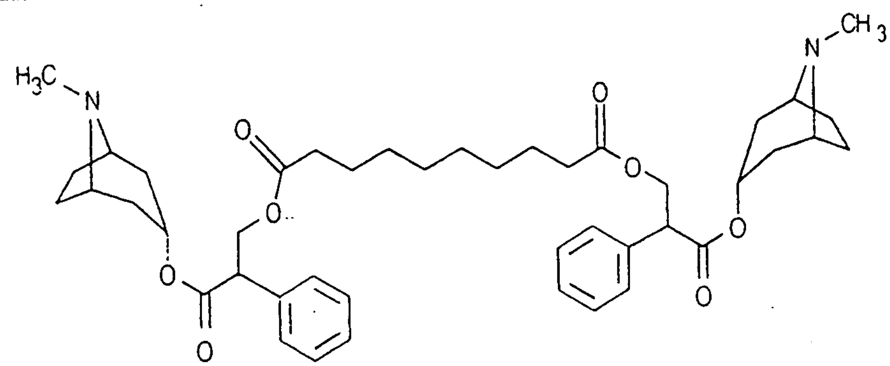
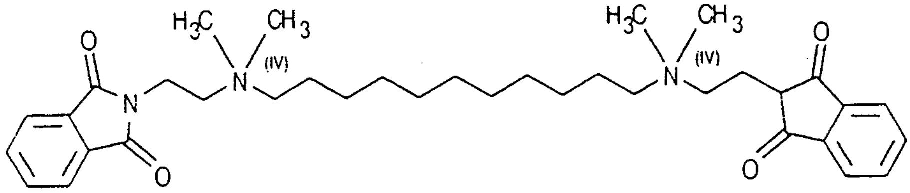
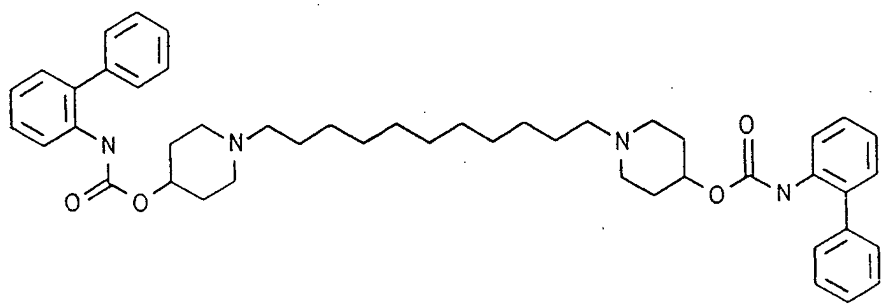
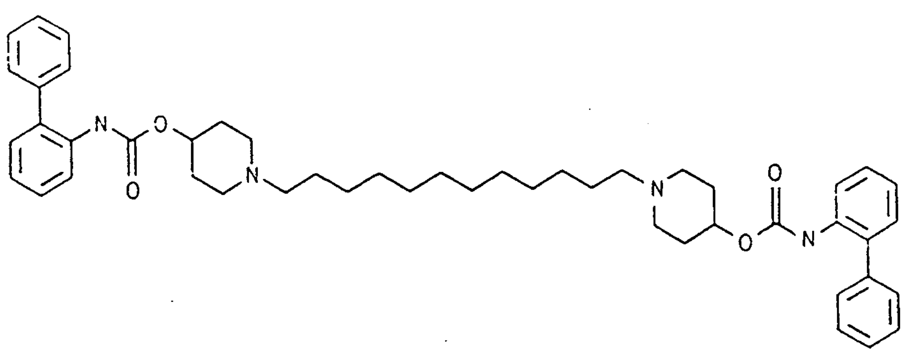
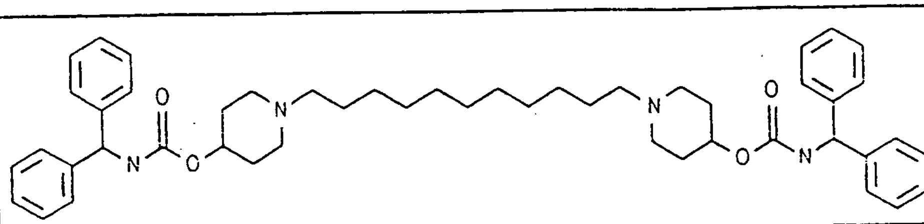
126	
127	
128	
129	
130	

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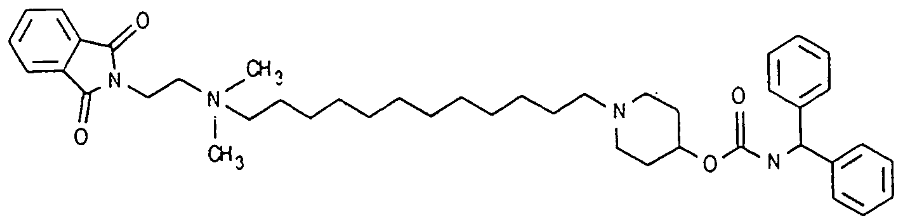
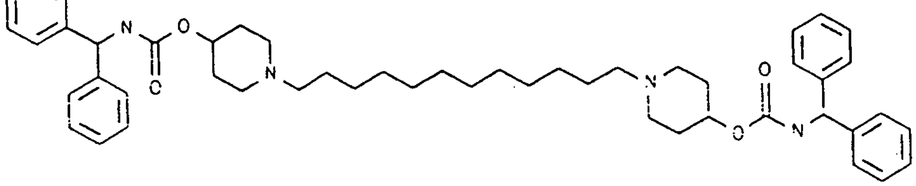
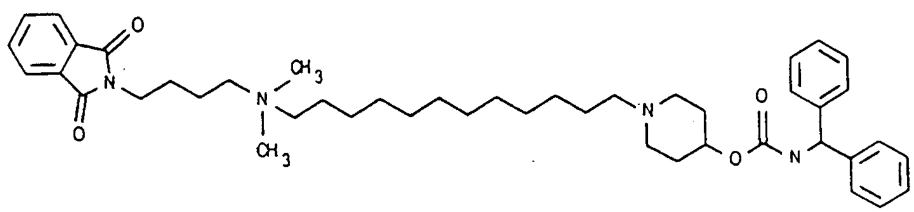
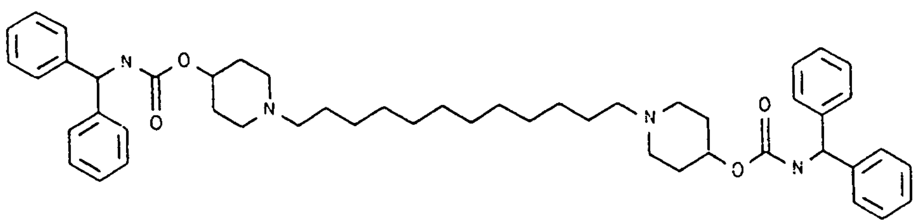
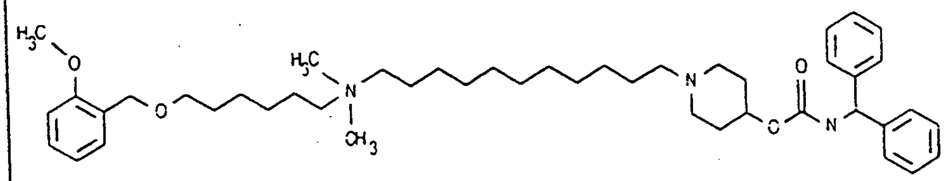
131	
132	
133	
134	
135	

TABLE 3

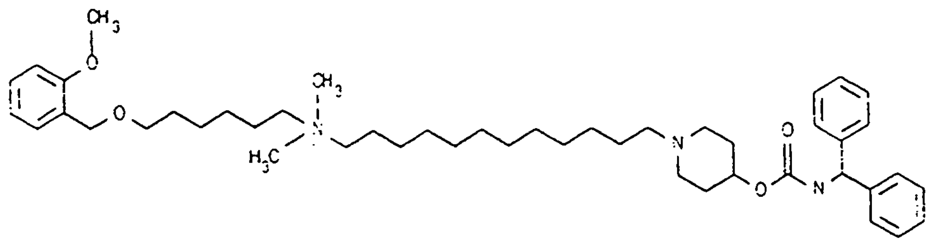
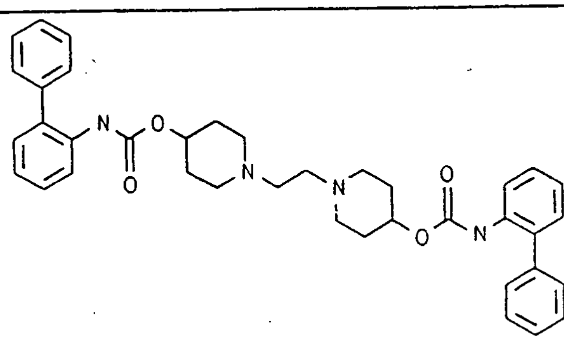
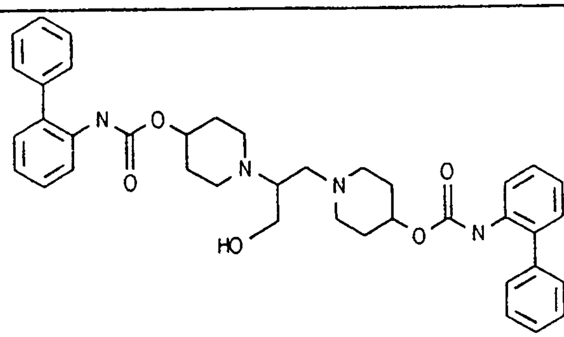
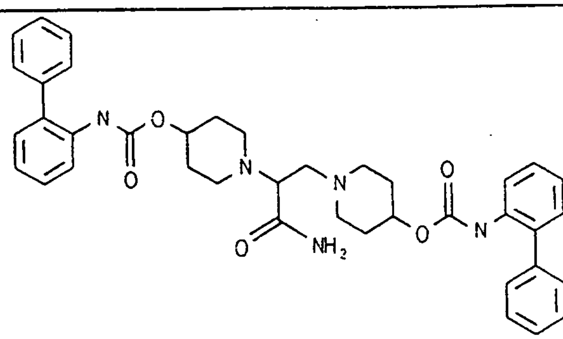
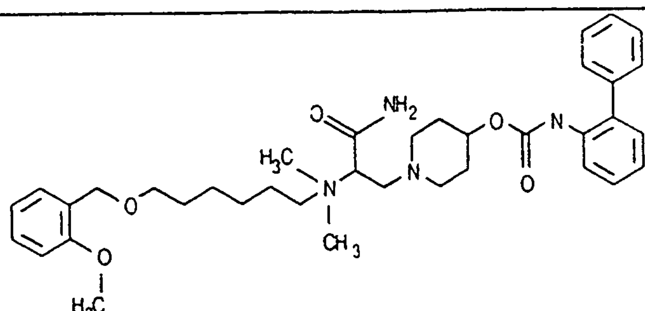
#	STRUCTURE
136	
137	
138	
139	
140	

TABLE 3

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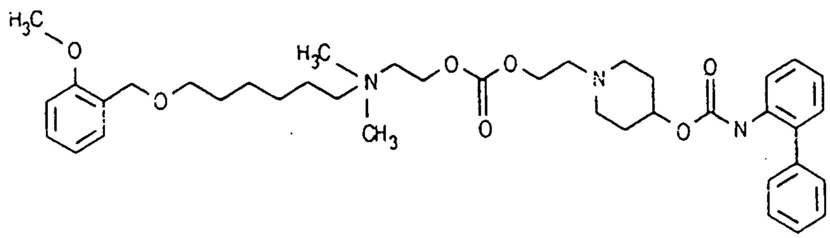
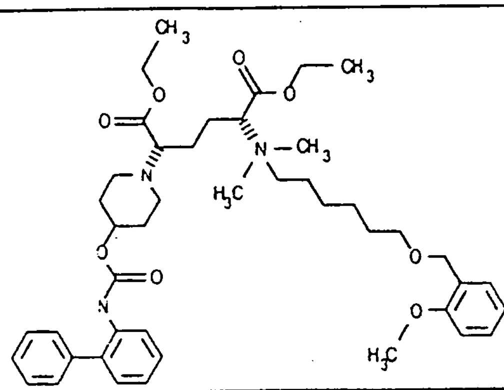
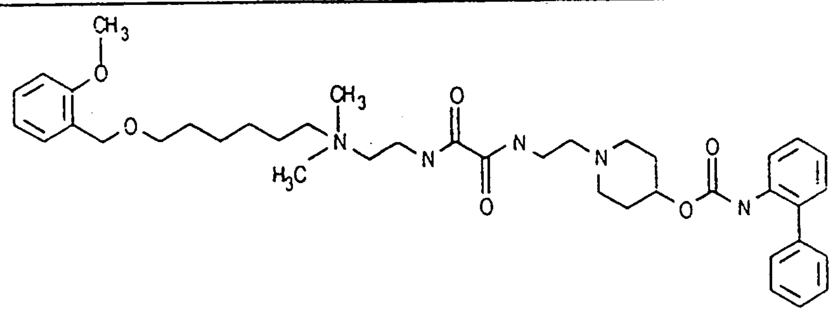
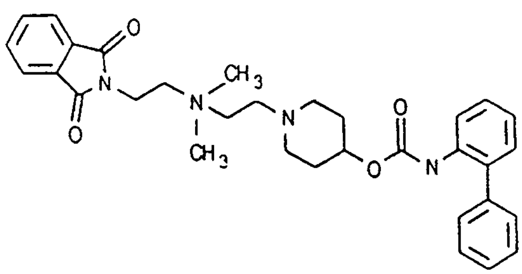
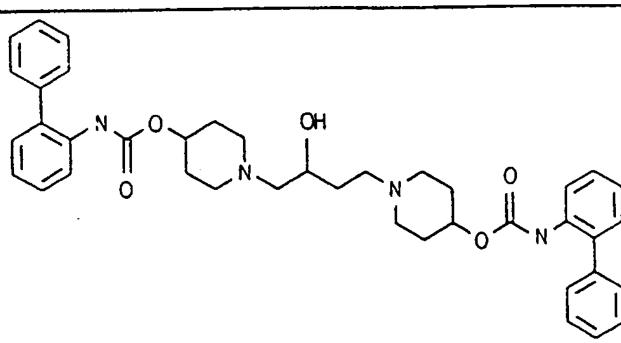
141	
142	
143	
144	
145	

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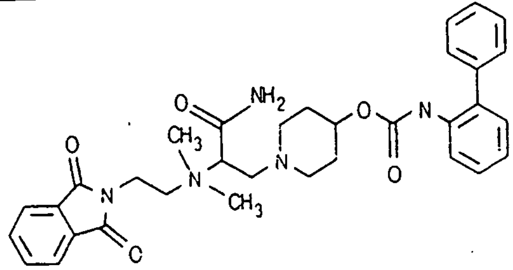
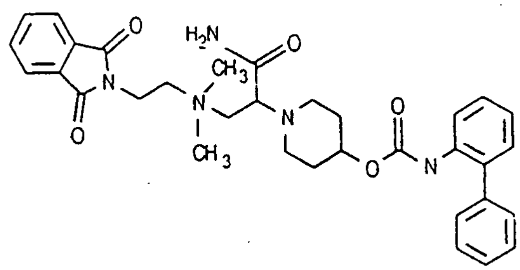
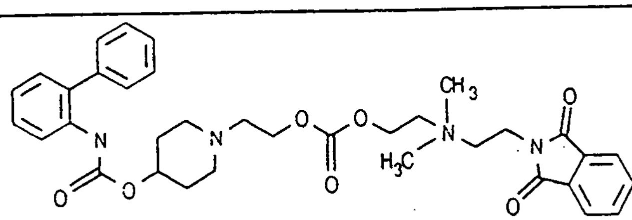
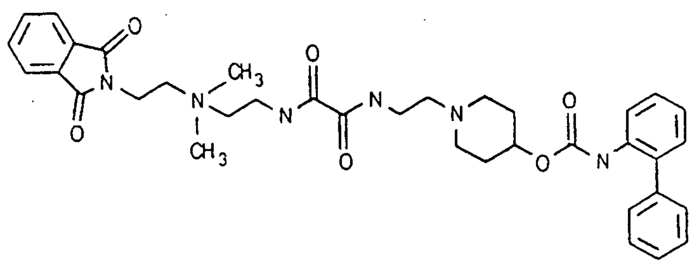
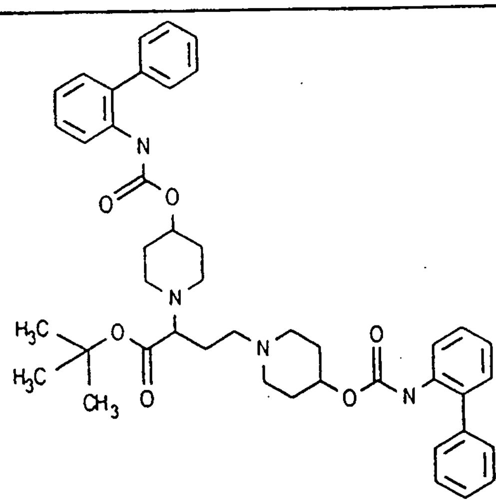
146	
147	
148	
149	
150	

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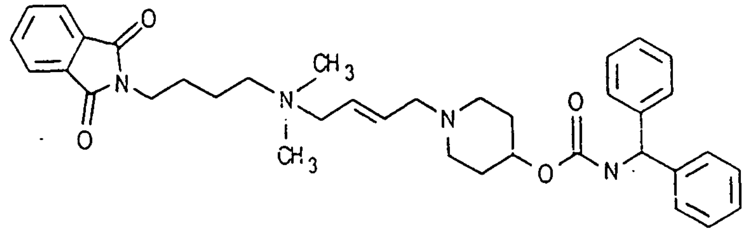
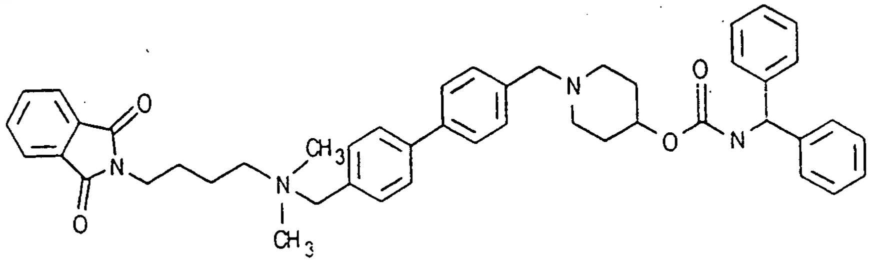
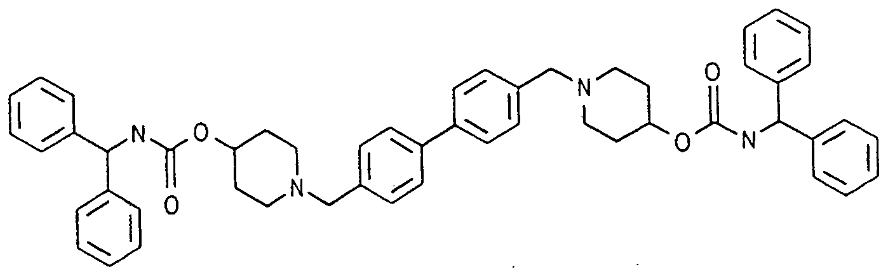
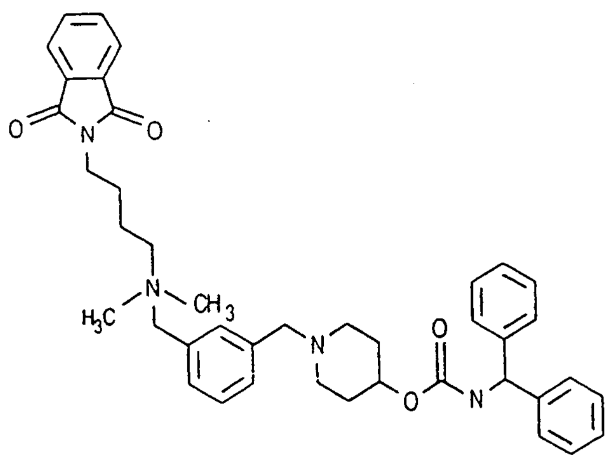
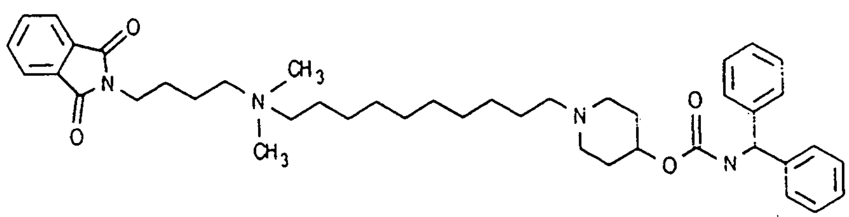
151	
152	
153	
154	
155	

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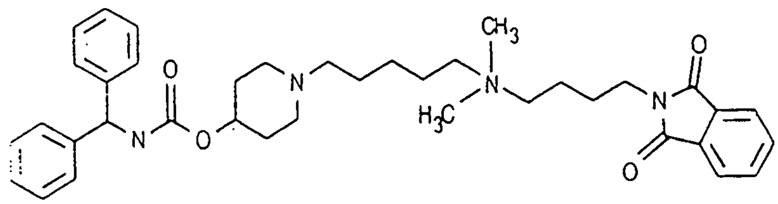
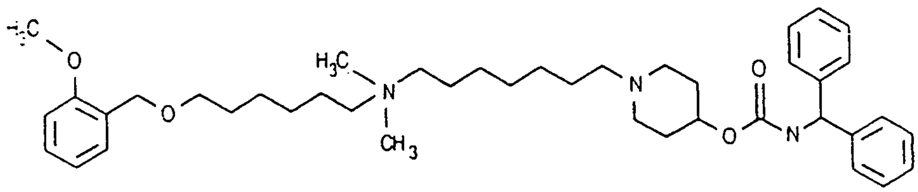
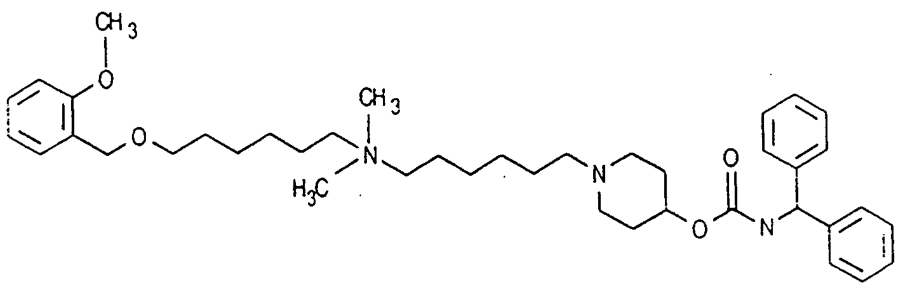
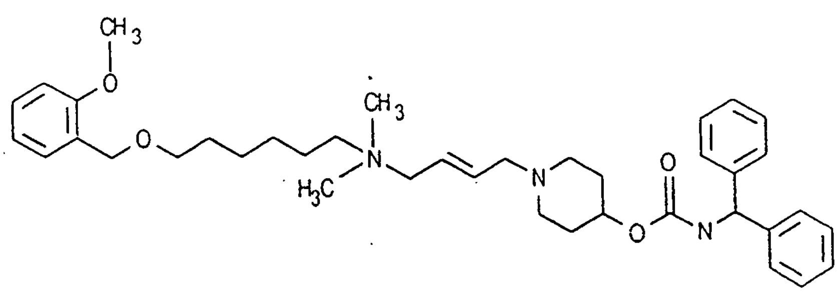
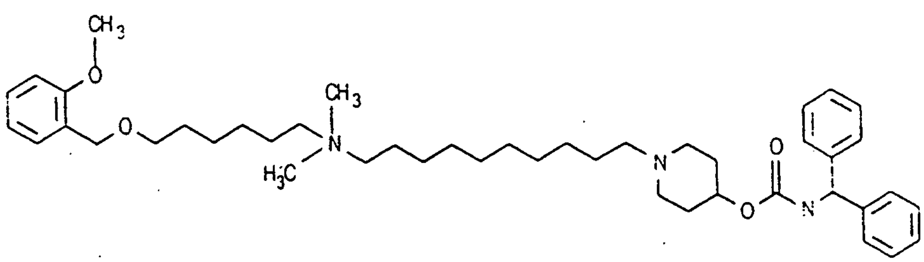
156	
157	
158	
159	
160	

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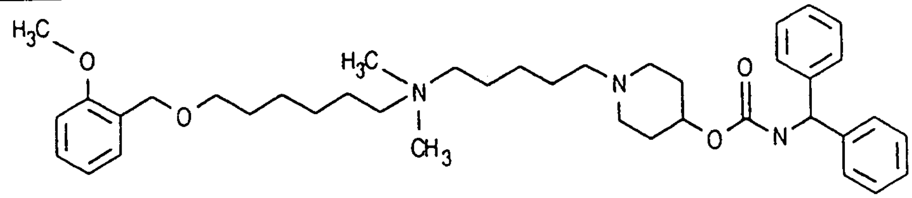
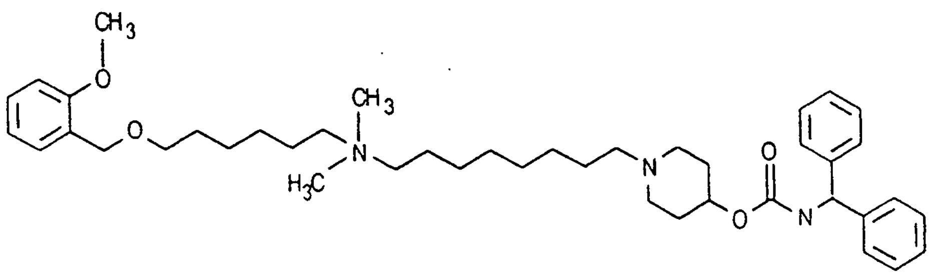
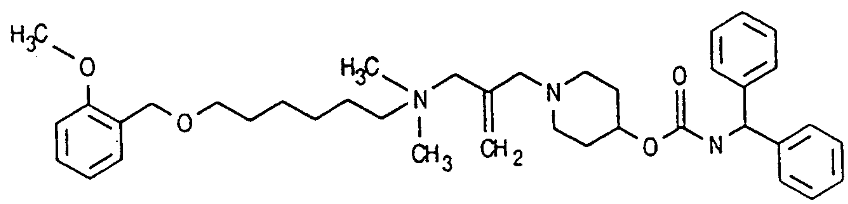
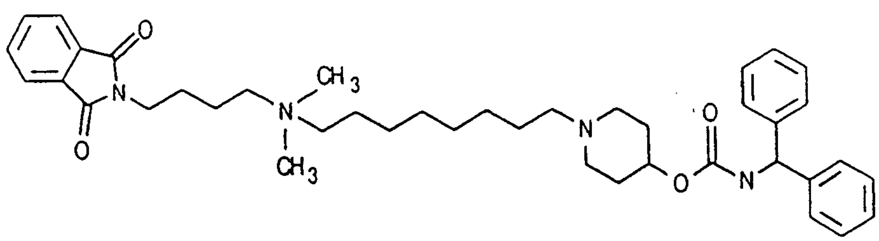
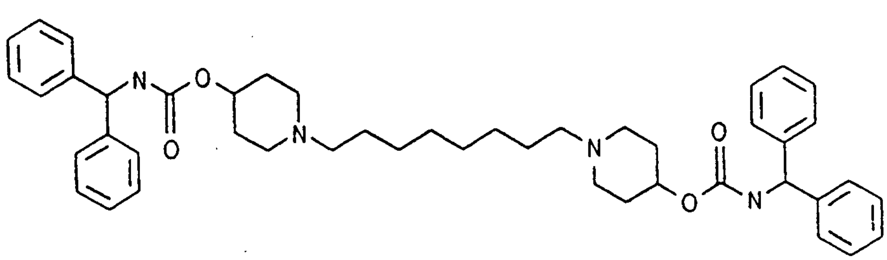
161	
162	
163	
164	
165	

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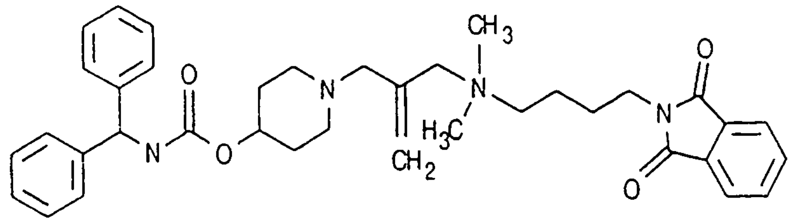
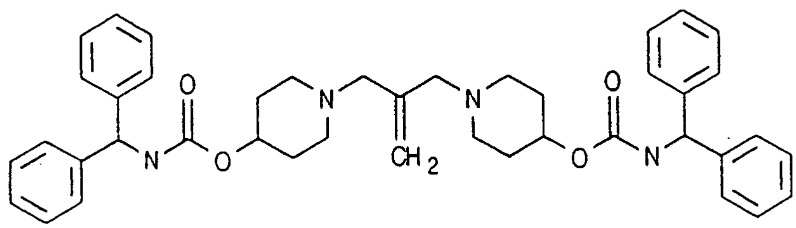
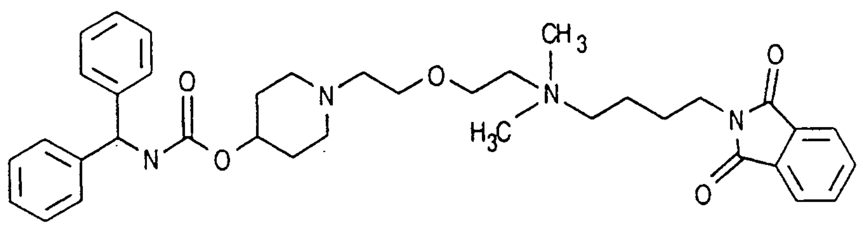
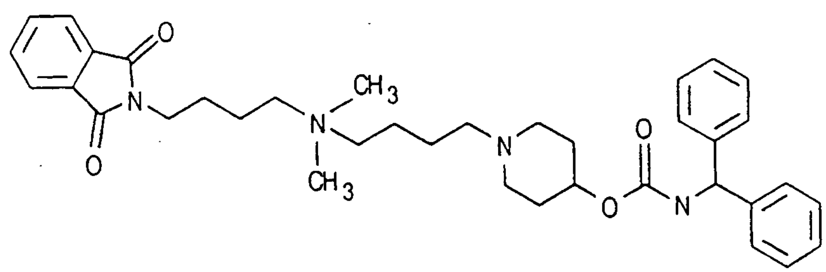
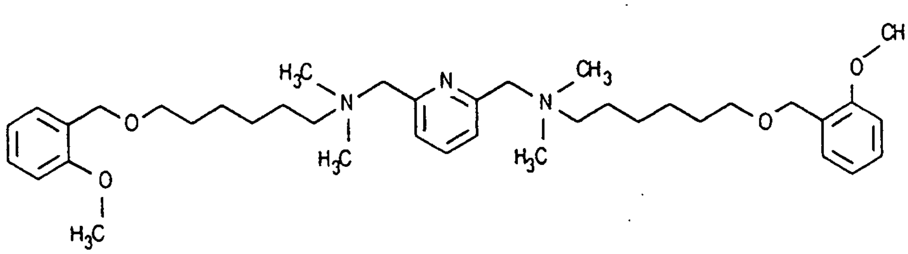
166	
167	
168	
169	
170	

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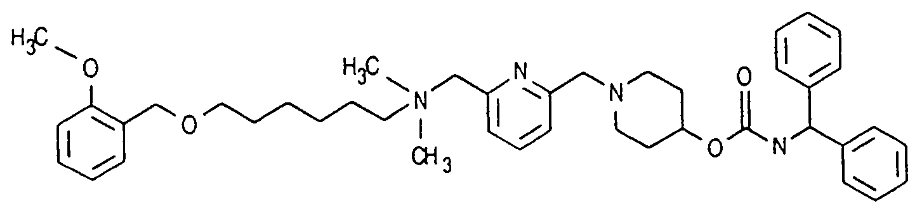
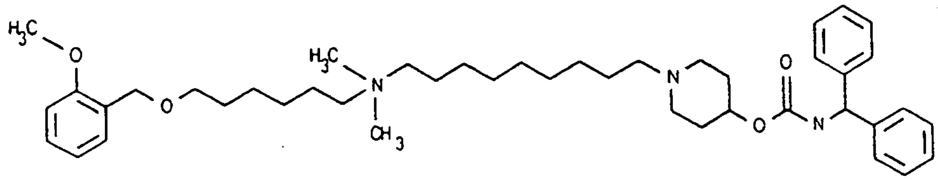
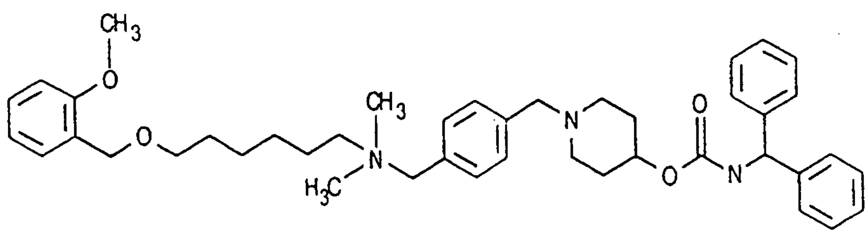
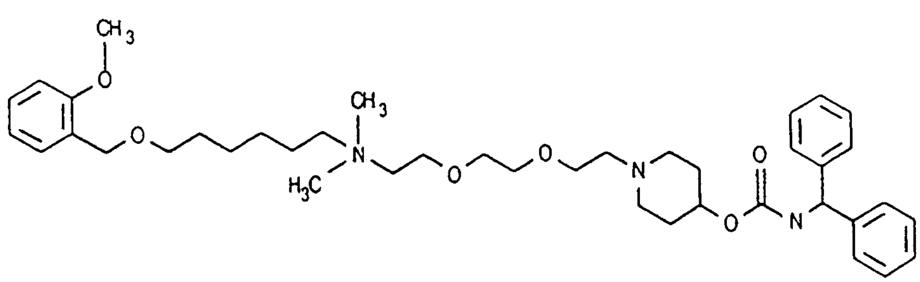
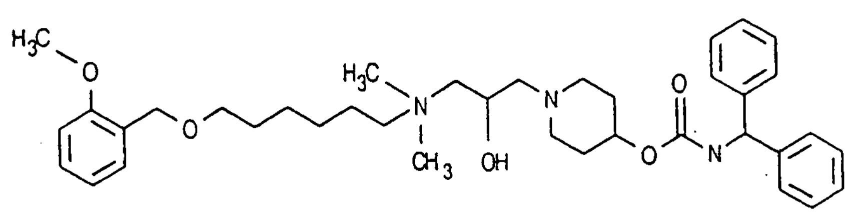
171	
172	
173	
174	
175	

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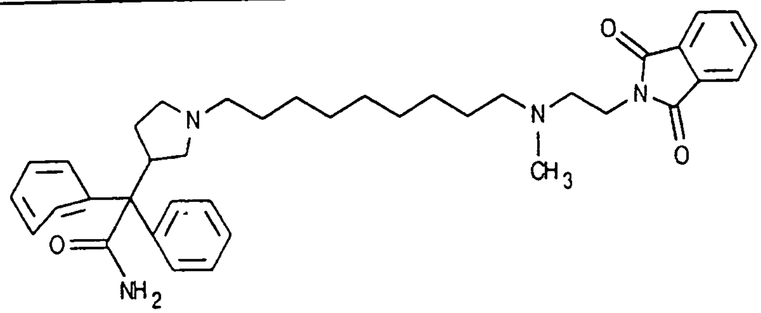
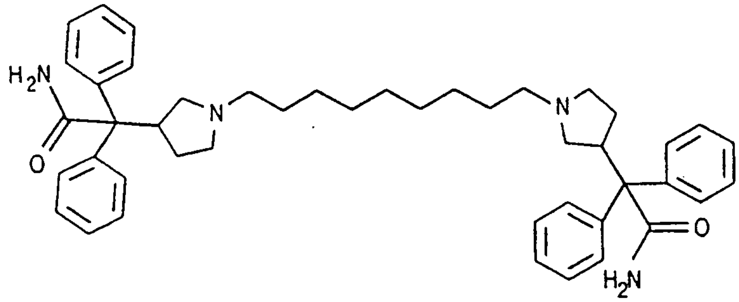
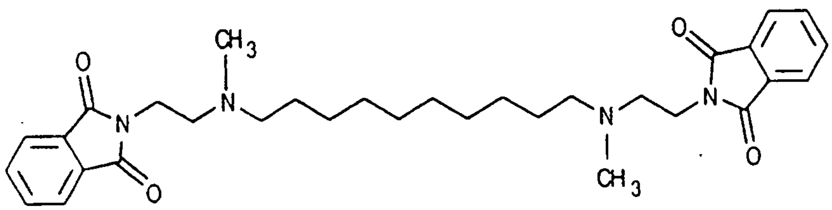
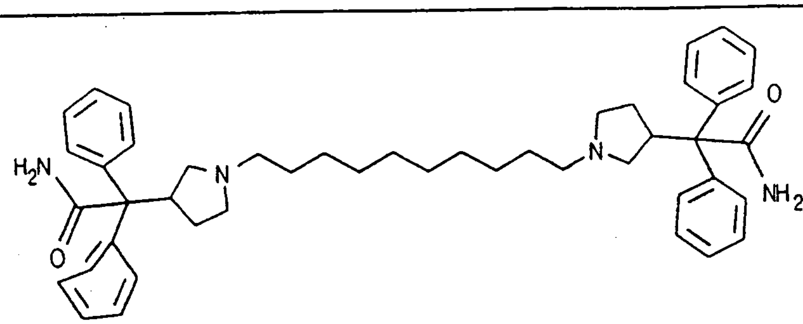
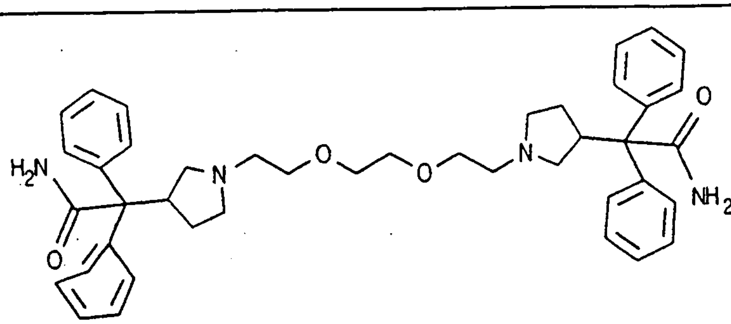
181	
182	
183	
184	
185	

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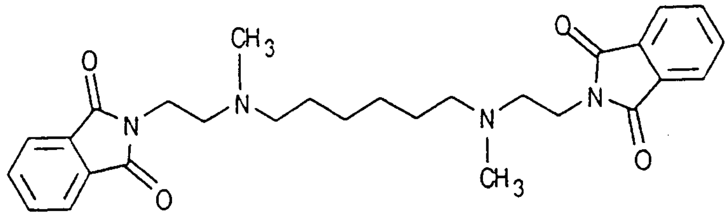
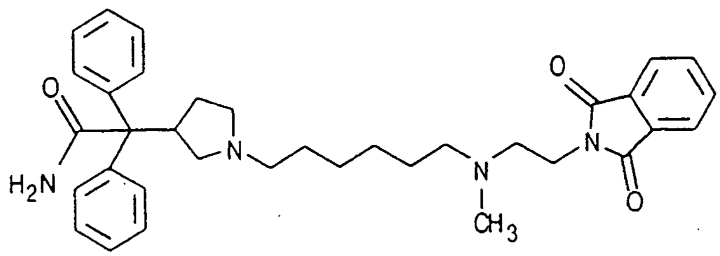
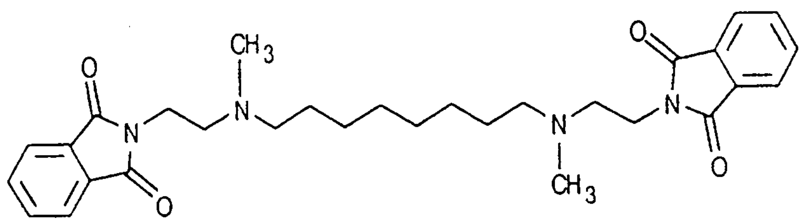
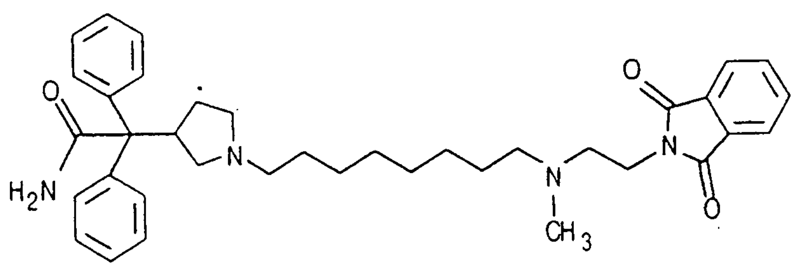
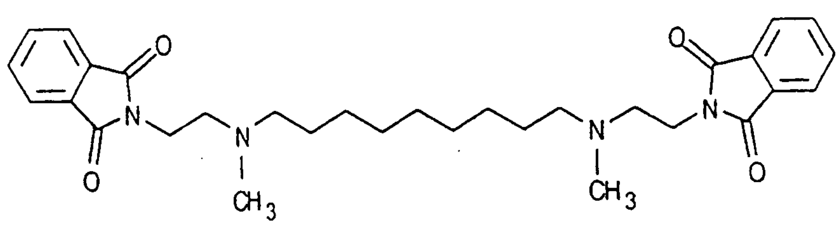
176	
177	
178	
179	
180	

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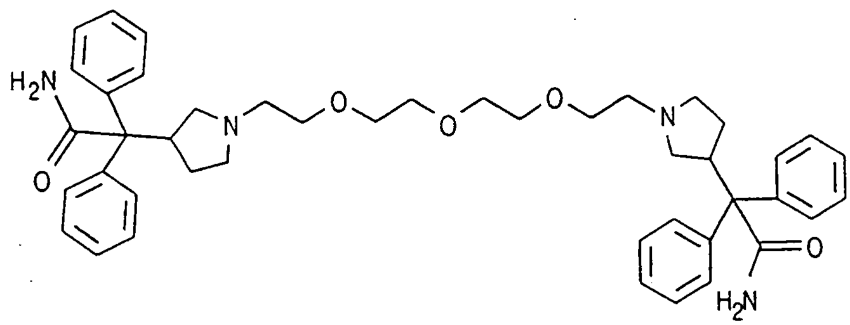
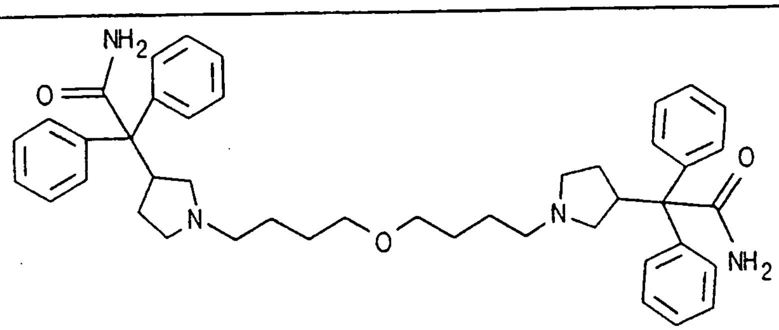
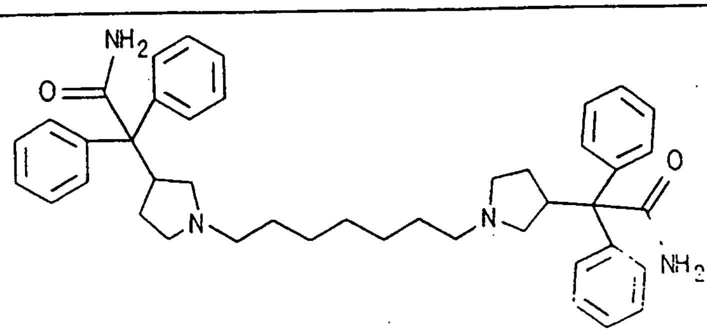
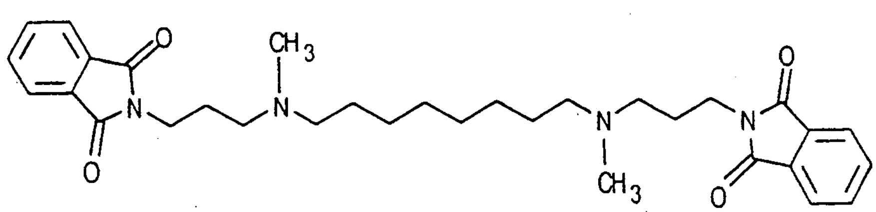
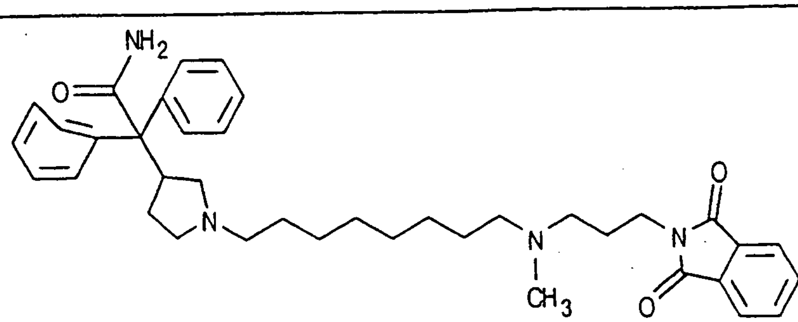
186	
187	
188	
189	
190	

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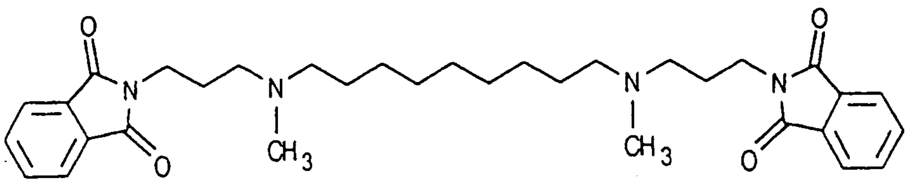
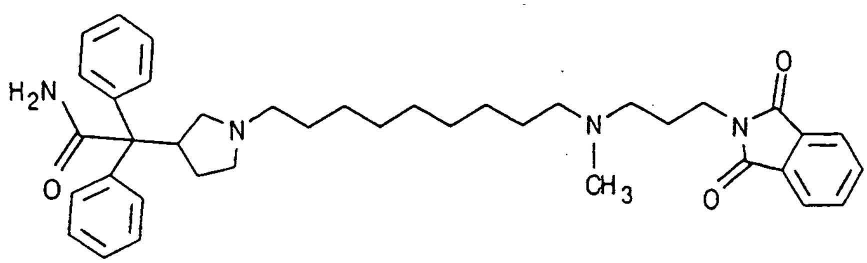
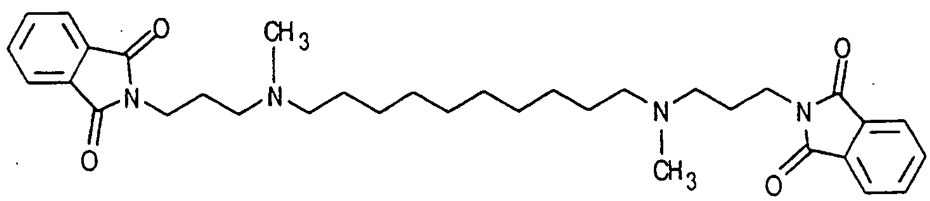
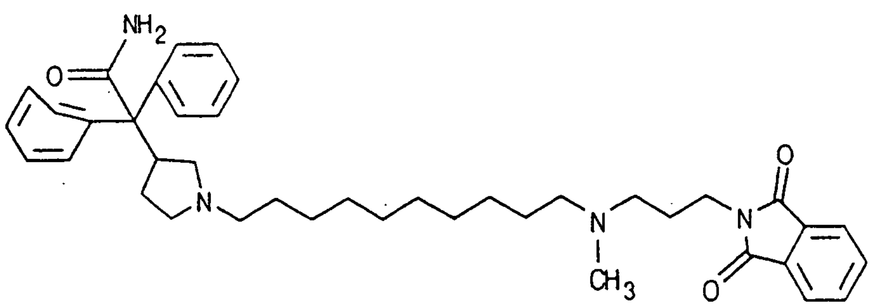
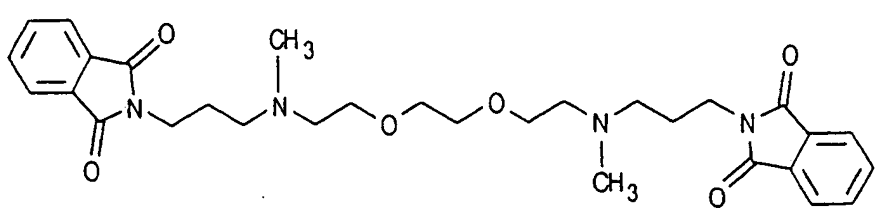
191	
192	
193	
194	
195	

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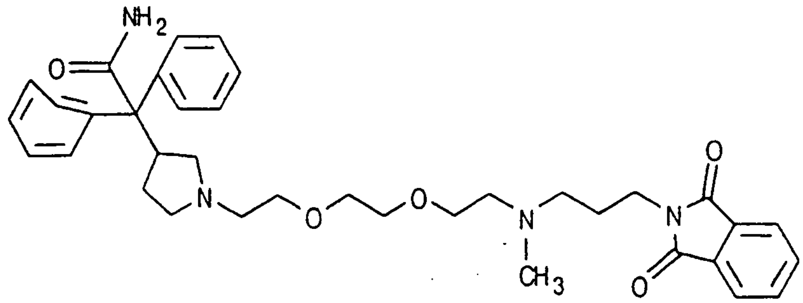
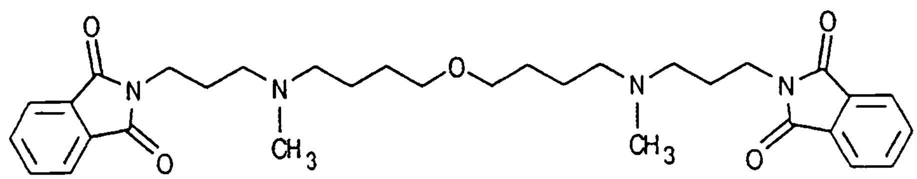
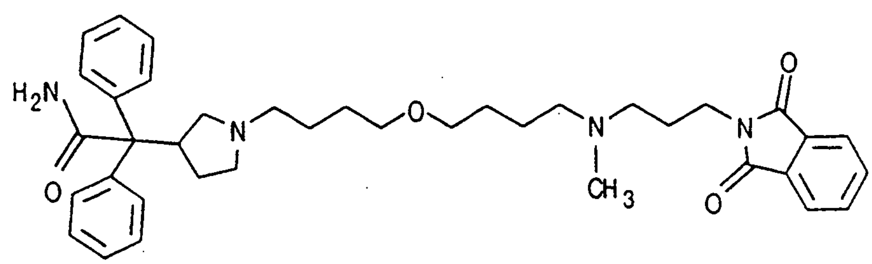
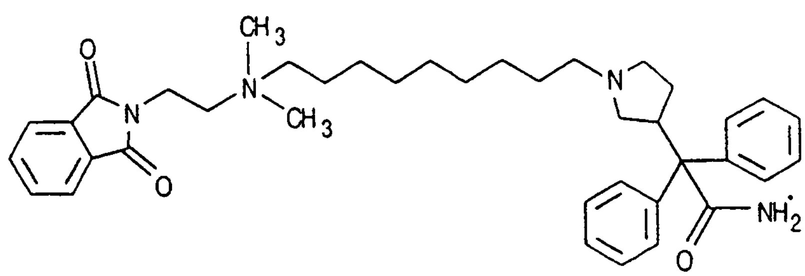
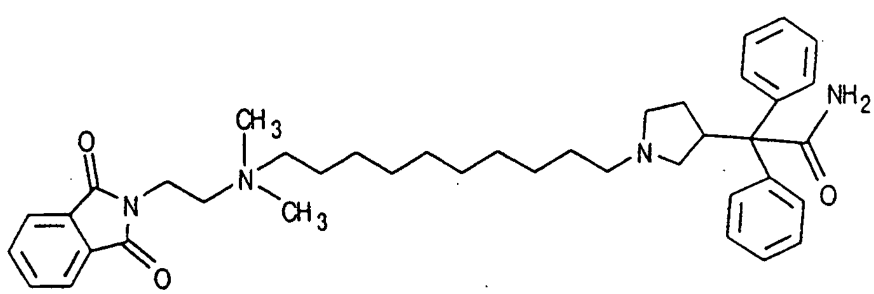
196	
197	
198	
199	
200	

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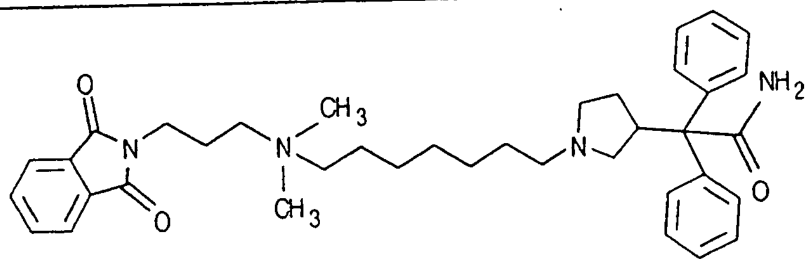
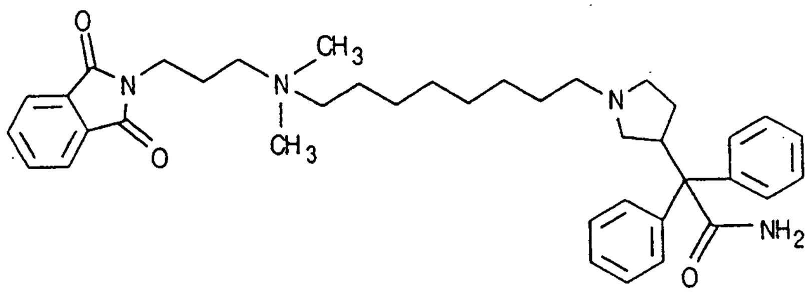
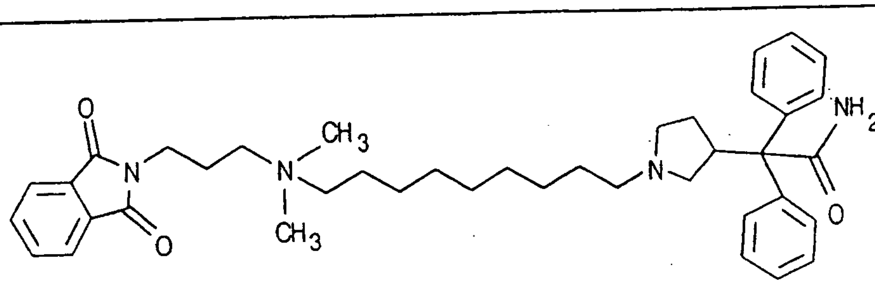
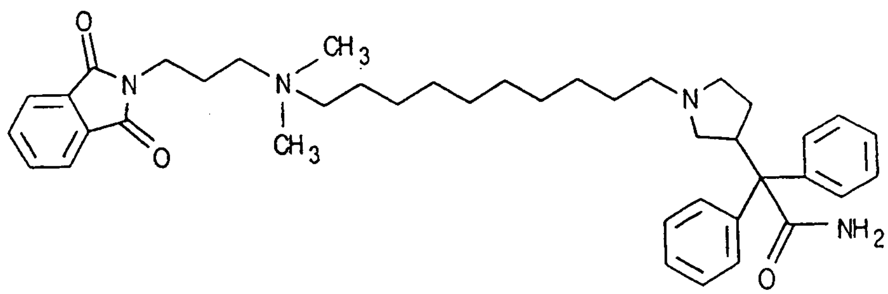
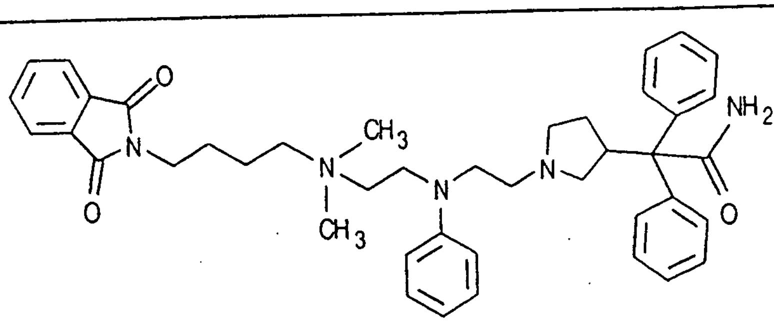
201	
202	
203	
204	
205	

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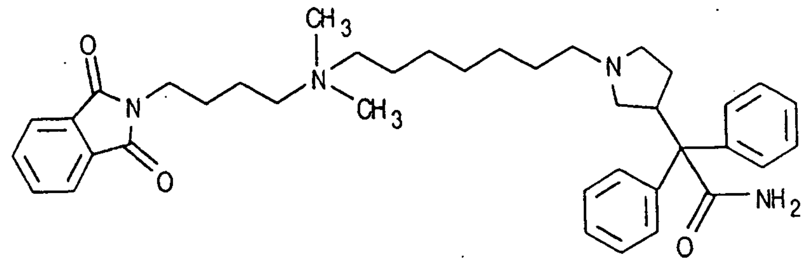
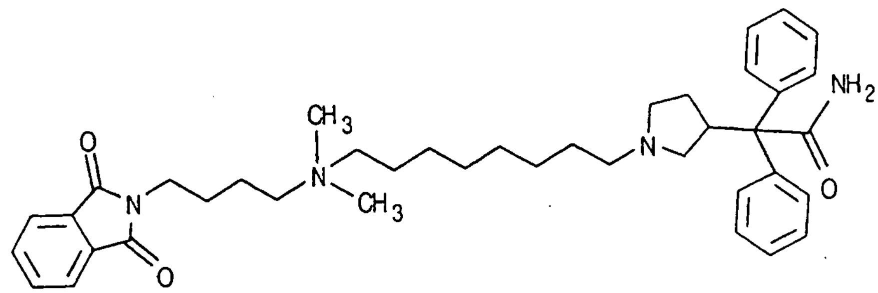
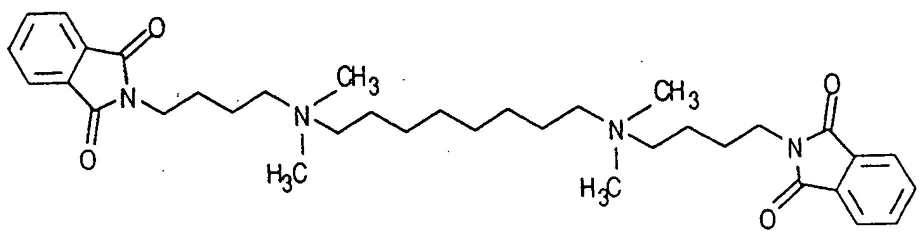
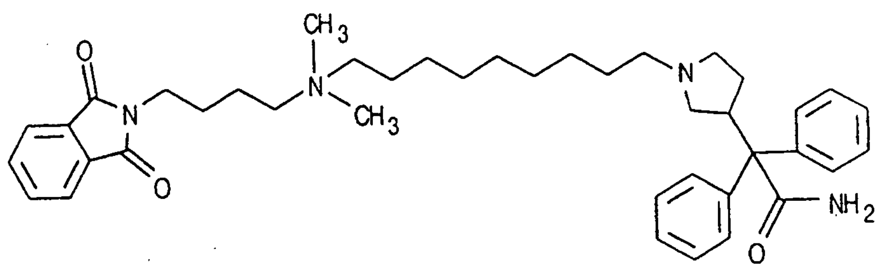
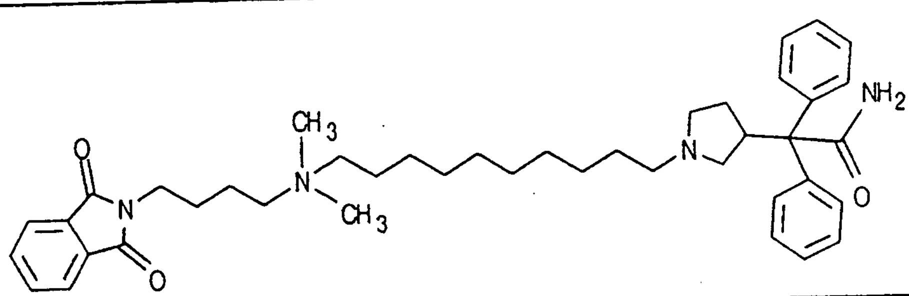
206	
207	
208	
209	
210	

TABLE 3

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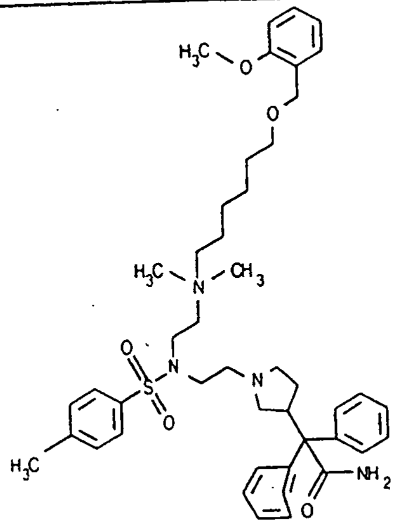
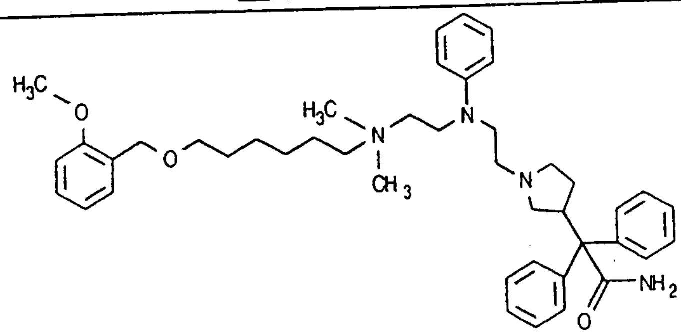
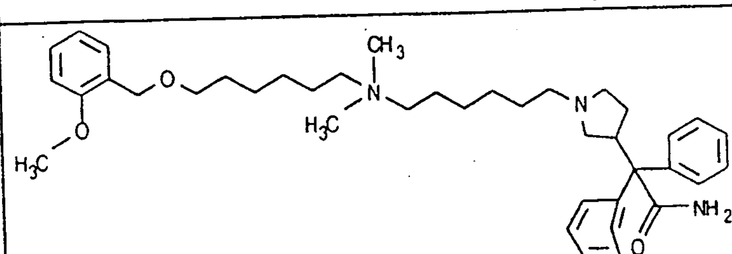
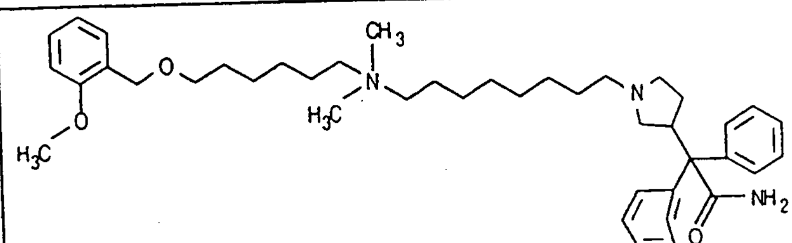
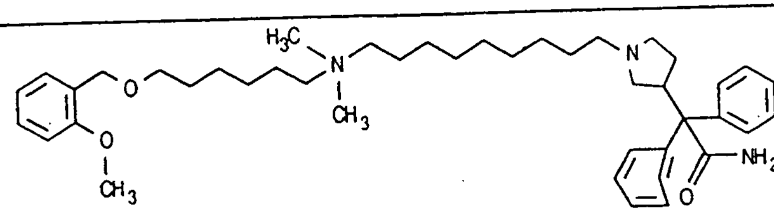
211	
212	
213	
214	
215	

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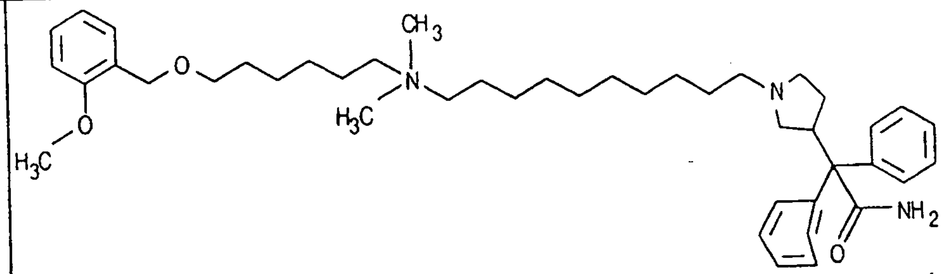
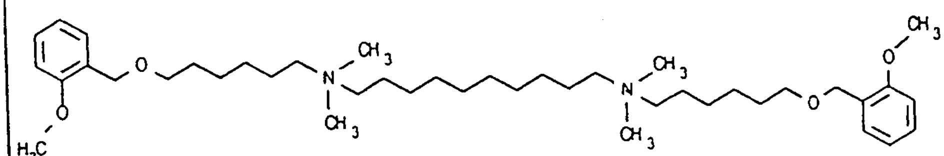
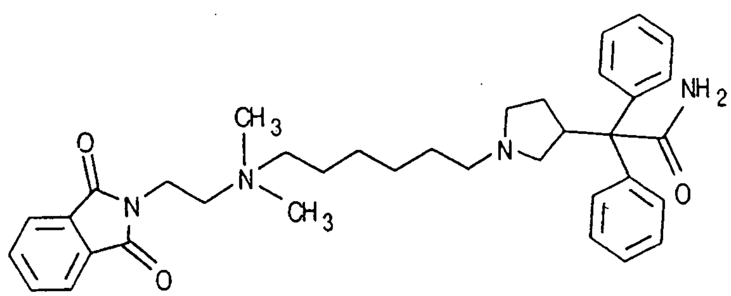
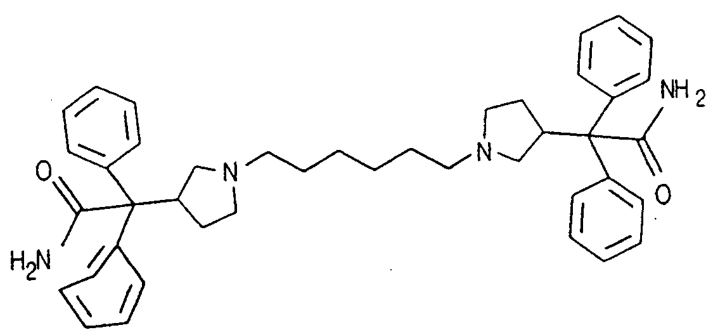
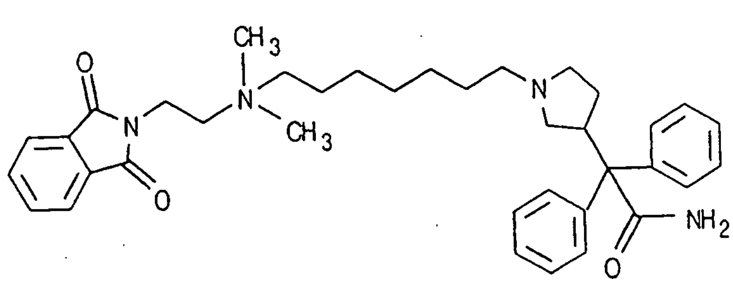
216	
217	
218	
219	
220	

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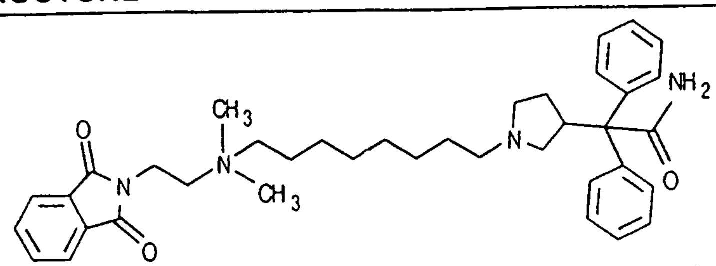
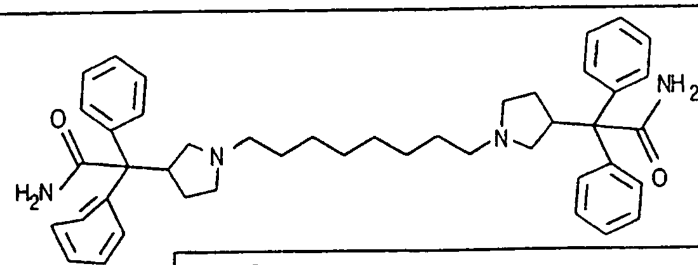
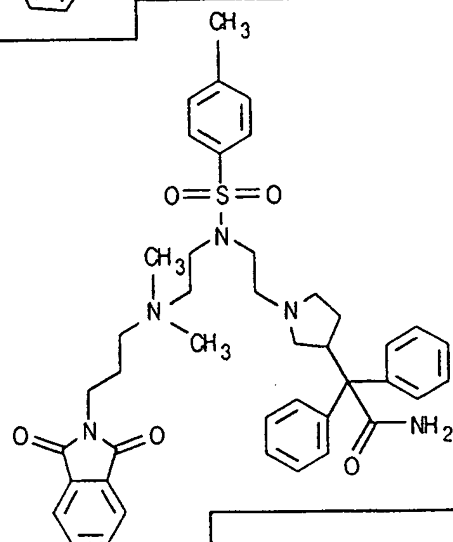
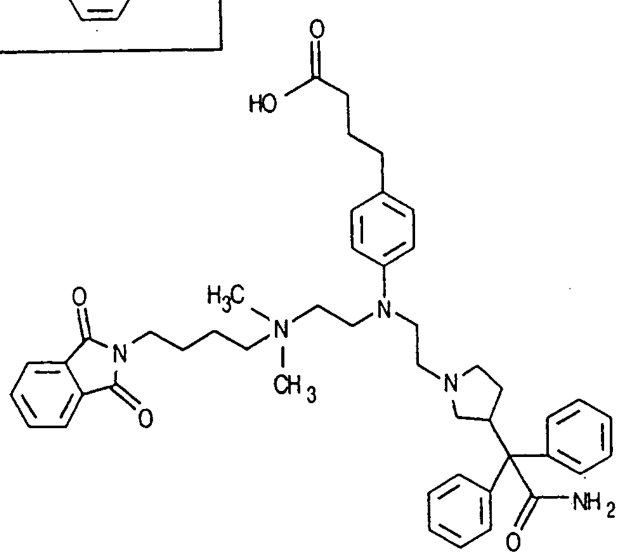
221	
222	
223	
224	

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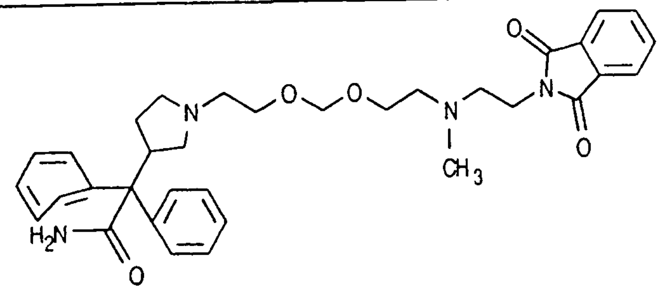
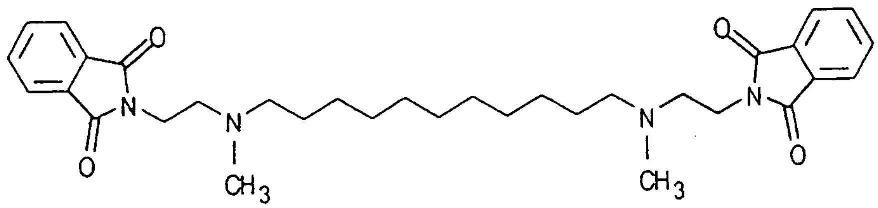
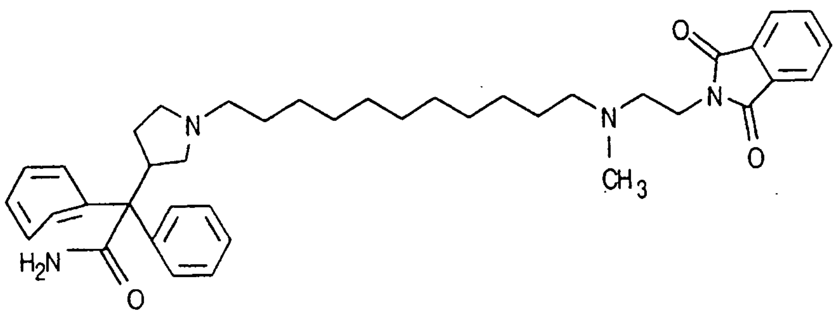
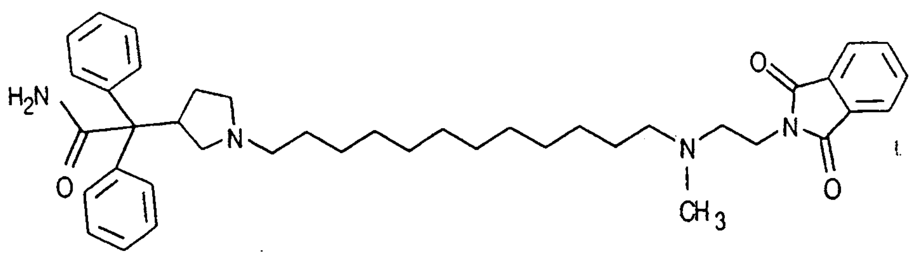
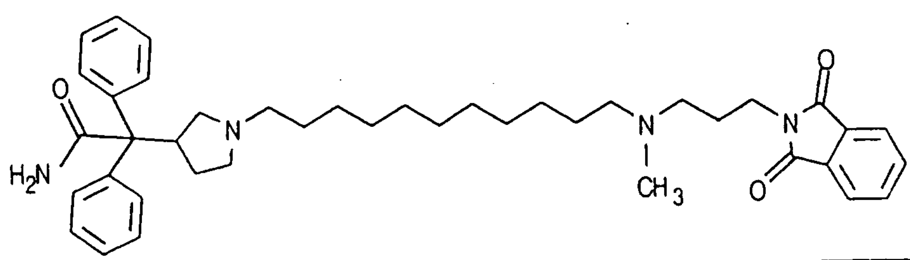
225	
226	
227	
228	
229	

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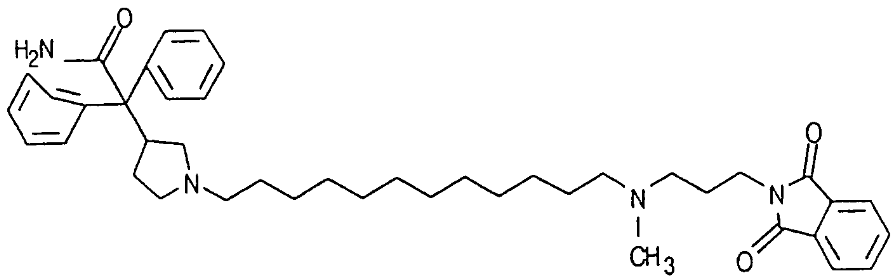
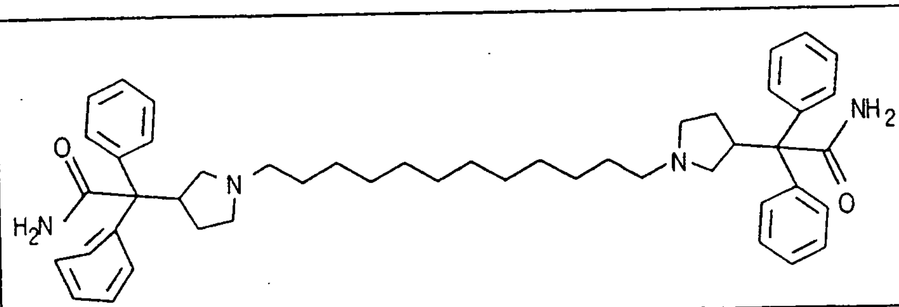
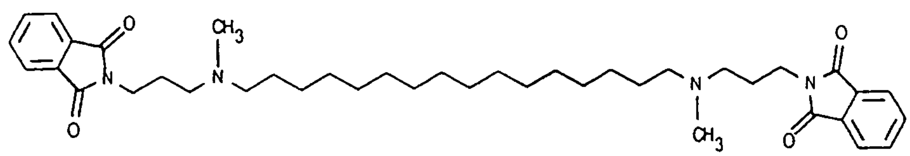
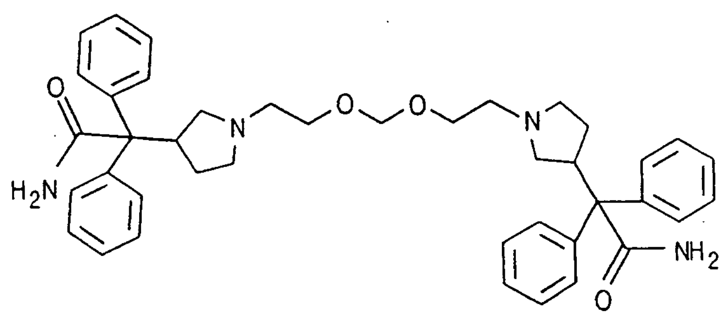
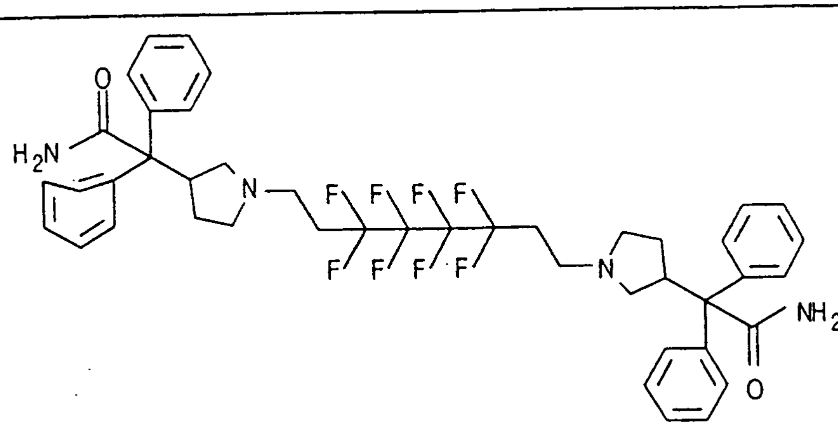
230	
231	
232	
233	
234	

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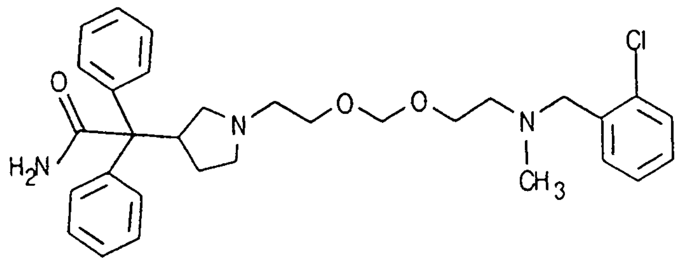
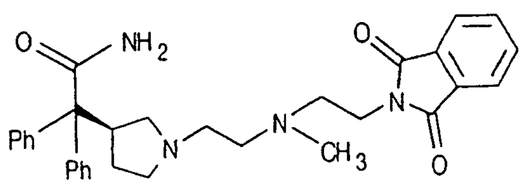
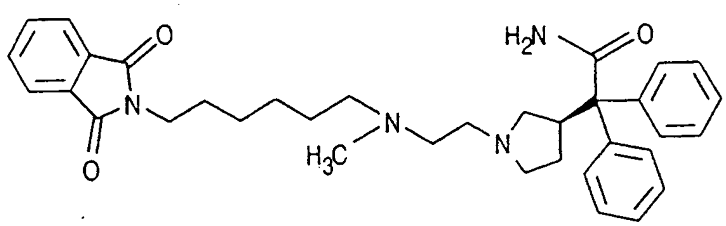
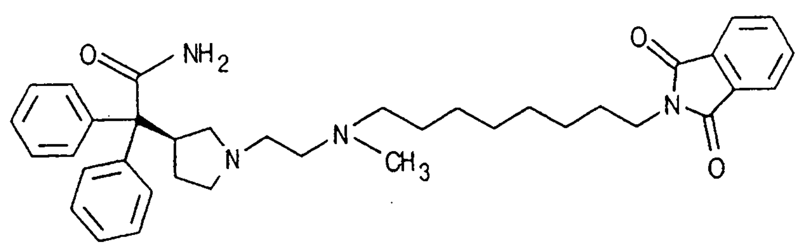
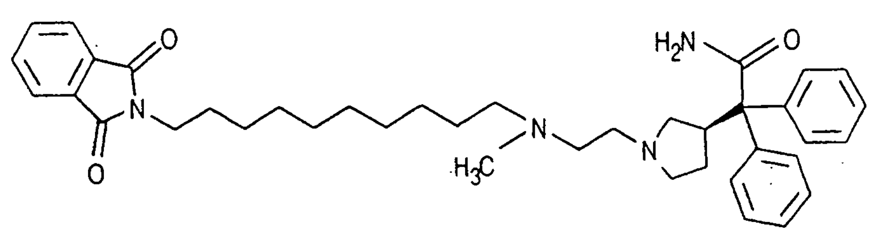
235	
236	
237	
238	
239	

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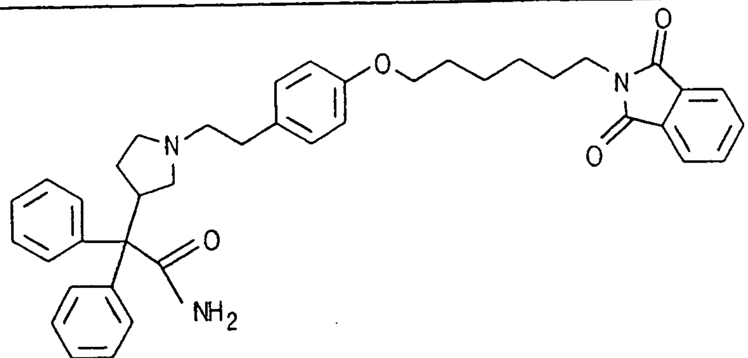
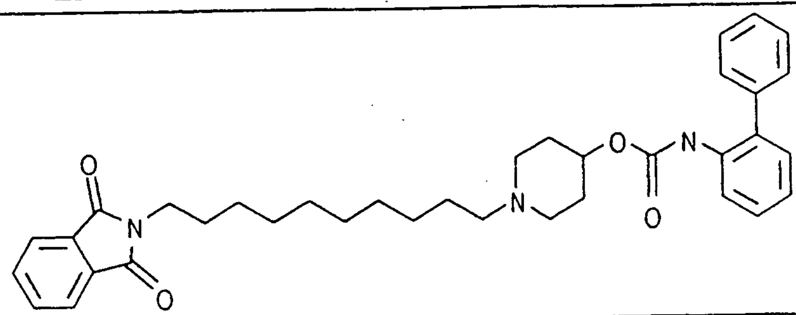
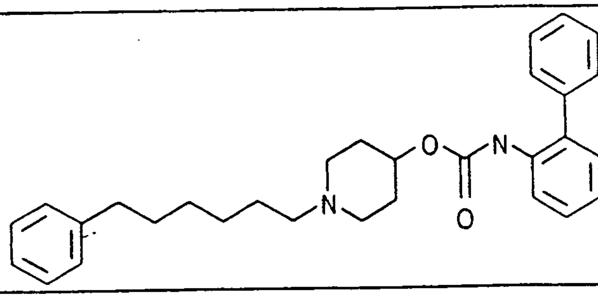
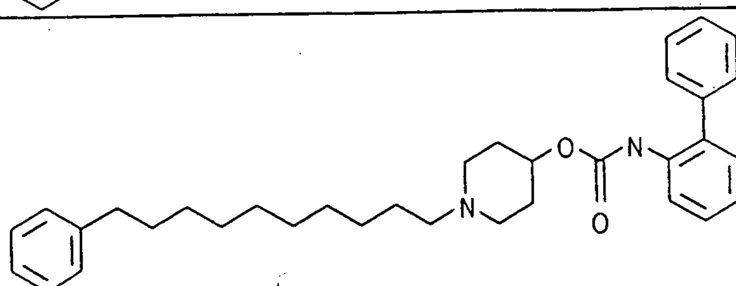
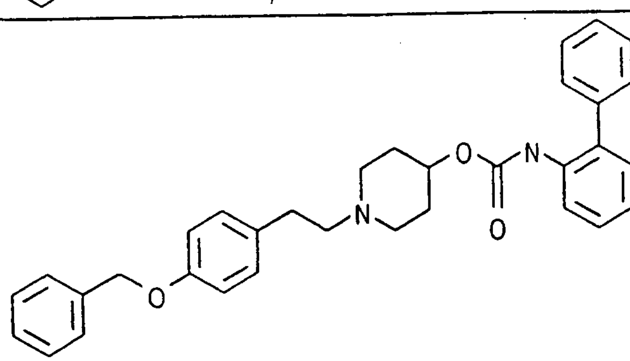
240	
241	
242	
243	
244	

Formulation Examples

Example 9

Hard gelatin capsules containing the following ingredients are prepared:

Ingredient	Quantity (mg/capsule)
Active Ingredient	30.0
Starch	305.0
Magnesium stearate	5.0

The above ingredients are mixed and filled into hard gelatin capsules in 340 mg quantities.

Example 10

A tablet Formula is prepared using the ingredients below:

Ingredient	Quantity (mg/tablet)
Active Ingredient	25.0
Cellulose, microcrystalline	200.0
Colloidal silicon dioxide	10.0
Stearic acid	5.0

The components are blended and compressed to form tablets, each weighing 240 mg.

Example 11

A dry powder inhaler formulation is prepared containing the following components:

Ingredient	Weight %
Active Ingredient	5
Lactose	95

The active ingredient is mixed with the lactose and the mixture is added to a dry powder inhaling appliance.

Example 12

Tablets, each containing 30 mg of active ingredient, are prepared as follows:

Ingredient	Quantity (mg/tablet)
Active Ingredient	30.0 mg
Starch	45.0 mg
Microcrystalline cellulose	35.0 mg
Polyvinylpyrrolidone (as 10% solution in sterile water)	4.0 mg
Sodium carboxymethyl starch	4.5 mg
Magnesium stearate	0.5 mg
Talc	1.0 mg
Total	120 mg

The active ingredient, starch and cellulose are passed through a No. 20 mesh U.S. sieve and mixed thoroughly. The solution of polyvinylpyrrolidone is mixed with the resultant powders, which are then passed through a 16 mesh U.S. sieve. The granules so produced are dried at 50° to 60°C and passed through a 16 mesh U.S. sieve. The sodium carboxymethyl starch, magnesium stearate, and talc, previously passed through a No. 30 mesh U.S. sieve, are then added to the granules which, after mixing, are compressed on a tablet machine to yield tablets each weighing 120 mg.

Example 13

Capsules, each containing 40 mg of medicament are made as follows:

Ingredient	Quantity (mg/capsule)
Active Ingredient	40.0 mg
Starch	109.0 mg
Magnesium stearate	1.0 mg
Total	150.0 mg

The active ingredient, starch, and magnesium stearate are blended, passed through a No. 20 mesh U.S. sieve, and filled into hard gelatin capsules in 150 mg

quantities.

Example 14

Suppositories, each containing 25 mg of active ingredient are made as follows:

Ingredient	Amount
Active Ingredient	25 mg
Saturated fatty acid glycerides to	2,000 mg

The active ingredient is passed through a No. 60 mesh U.S. sieve and suspended in the saturated fatty acid glycerides previously melted using the minimum heat necessary. The mixture is then poured into a suppository mold of nominal 2.0 g capacity and allowed to cool.

Example 15

Suspensions, each containing 50 mg of medicament per 5.0 mL dose are made as follows:

Ingredient	Amount
Active Ingredient	50.0 mg
Xanthan gum	4.0 mg
Sodium carboxymethyl cellulose (11%)	
Microcrystalline cellulose (89%)	50.0 mg
Sucrose	1.75 g
Sodium benzoate	10.0 mg
Flavor and Color	q.v.
Purified water to	5.0 mL

The active ingredient, sucrose and xanthan gum are blended, passed through a No. 10 mesh U.S. sieve, and then mixed with a previously made solution of the microcrystalline cellulose and sodium carboxymethyl cellulose in water. The sodium benzoate, flavor, and color are diluted with some of the water and added with stirring. Sufficient water is then added to produce the required volume.

Example 16

A formulation may be prepared as follows:

Ingredient	Quantity (mg/capsule)
Active Ingredient	15.0 mg
Starch	407.0 mg
Magnesium stearate	3.0 mg
Total	425.0 mg

The active ingredient, starch, and magnesium stearate are blended, passed through a No. 20 mesh U.S. sieve, and filled into hard gelatin capsules in 425.0 mg quantities.

Example 17

A formulation may be prepared as follows:

Ingredient	Quantity
Active Ingredient	5.0 mg
Corn Oil	1.0 mL

Example 18

A topical formulation may be prepared as follows:

Ingredient	Quantity
Active Ingredient	1-10 g
Emulsifying Wax	30 g
Liquid Paraffin	20 g
White Soft Paraffin	to 100 g

The white soft paraffin is heated until molten. The liquid paraffin and emulsifying wax are incorporated and stirred until dissolved. The active ingredient is added and stirring is continued until dispersed. The mixture is then cooled until solid.

Another preferred formulation employed in the methods of the present invention employs transdermal delivery devices ("patches"). Such transdermal patches may be used to provide continuous or discontinuous infusion of the

compounds of the present invention in controlled amounts. The construction and use of transdermal patches for the delivery of pharmaceutical agents is well known in the art. *See, e.g.*, U.S. Patent 5,023,252, issued June 11, 1991, herein incorporated by reference in its entirety. Such patches may be constructed for continuous, pulsatile, or on demand delivery of pharmaceutical agents.

Other suitable formulations for use in the present invention can be found in *Remington's Pharmaceutical Sciences*, edited by E. W. Martin (Mack Publishing Company, 18th ed., 1990).

Biological Examples

Example 19

M_3 Muscarinic Receptor In Vitro Binding Assay

The M_3 muscarininc receptor binding activity of compounds of the invention was tested as follows:

SF9 cell membranes containing human M_3 muscarinic receptor was obtained from NEN (Boston, MA). In 96-well microtiter plates, eight serial five-fold dilutions were prepared with the compound to be assayed; the highest concentration was typically 4μM (4x the final concentration). To 100 μl of compound dilution was added 150 μL M_3 receptor membrane preparation in PBS/1.0mM $MgCl_2$/pH 7.4. 50 μl of 3.2 nM 3H-N-methylscopolamine radioligand was added. The total volume in each well was then 300μl. The filter plate was pre-blocked using 0.3% PEI for at least 15 minutes, and then washed twice with 200 μl PBS. The assay plate was incubated for 1 hour at room temperature with gentle shaking. The contents of the assay plate were then transferred to the filter plate, and washed three times using 200μl PBS. About 40 μl of scint was added to each well and then the plate was allowed to sit at room temperature for 2h, and then counted using a Packard Topcount NXT. Counting was typically performed for 1minute per well using a standard protocol on a Packard top counter. The raw data was fit to a standard 4-parameter equation given below and a value of IC50 obtained.

$Y=(a-d)/(1+(x/c)^b) + d$ where

Y = cpm	a = total binding	b = slope
c = IC50	x = [compound]	d = nonspecific binding

A similar protocol was used to measure M1, M2, M4 and M5 human muscarinic receptor activity.

Example 20

Rat Heart Muscarinic Receptor In Vitro Binding Assay

Tissue (rat heart) muscarininc receptor binding activity of compounds of the invention was tested as follows:

First, muscarinic receptor enriched membranes were isolated from whole hearts (Pelfreeze Laboratories). Rat heart tissue was typically prepared as follows. 25 µl of ice cold buffer (20mM HEPES, 100mM NaCl/10mM $MgCl_2$ at pH 7.5 with "Complete" protease inhibitor cocktail purchased from Boehringer Mannheim was added into an oakridge tube. To the tube was then added 2g of rat heart (purchased from Harlan). The contents of the tube were then transferred to a wheaton glass cylinder and homogenized using a Polytron homogenizer (setting 22, 15 seconds x2), and then transferred back to the oakridge tube, and centrifuged for 10 minutes at 1500g. The supernatant was removed and then centrifuged for 20 minutes at 45000g. The supernatant was removed and the pellet resuspended in 5mL buffer and transferred to a wheaton glass cylinder. This material was then homogenized using a Potter type glass teflon homogenizer with 7-8 passes. The material is then transferred to an oakridge tube and the total volume brought up to 25mL. This volume is then centrifuged for 20 minutes at 45000g, and the pellet resuspended in 2mL buffer using 2 passes of a teflon homogenizer, and stored at -80 degrees C until used.

Second, a protocol similar to that used for cloned receptor binding was used: Eight serial five-fold dilutions are prepared with the compound to be assayed; the highest concentration was typically 4uM (4x the final concentration). To 50 µl of compound dilution in a 96-well assay plate is added an appropriate amount of rat

heart membrane (usually 12.5 µl of membrane prep in 87.5 µl of 20mM HEPES, 100mM NaCl/10mM $MgCl_2$ at pH 7.5). The amount of membrane added depends in general on the results of signal optimization, and ranges from 6.25-12.5 µl. Last, 50 µl of 2.12nM 3H-N-methylscopolamine radioligand was added. The total volume in each well was 200 µl. The filter plate was pre-blocked using 0.3% PEI for at least 15 minutes, and then washed twice with 200 µl PBS. The assay plate was incubated for 1 hour at room temperature with gentle shaking. The contents of the assay plate were then transferred to the filter plate, and washed three times using 200ul PBS. About 40 µl of scint was added to each well and then the plate was allowed to sit at room temperature for 18h, and then counted using a Packard Topcount NXT. Counting was typically performed for 1minute per well using a standard protocol on the Packard counter. The data was fit to the four parameter fit described above in Example 19.

A similar procedure was used to measure muscarinic receptor binding at rat submaxillary gland, rat bladder, guinea pig heart, guinea pig submaxillary gland, and guinea pig bladder.

Example 21

Rat Bladder M_3 In Vitro Binding Assay

Bladder was comprised of both M_2 and M_3 muscarinic receptors. The ratio was typically 4:1 M_2:M_3. In order to measure binding of test compounds to one of M_2 or M_3, the other was blocked with a reversible ligand that binds selectively to that receptor. The following example illustrates the procedure for M_3 bladder binding.

Membranes from rat bladder were prepared in a similar fashion to that used to isolate heart membrane above. Eight serial five-fold dilutions are prepared with the compound to be assayed in compound dilution buffer (20 mM HEPES/100mM NaCl/10mM $MgCl_2$/4 µM Methoctramine); the highest concentration was typically

4 μM (4x the final concentration). The concentration of methoctramine was sufficient to block >99% of the M2 receptor in bladder, but less than 40% of the M_3 receptor in bladder. To 50 μl of compound dilution in a 96-well assay plate is added an appropriate amount of rat heart membrane (usually 25 μl of membrane prep in 75 μl of 20mM HEPES, 100mM NaCl/10mM $MgCl_2$ at pH 7.5). The amount of membrane added depended in general on the results of signal optimization, and ranged from 12.5-25. Last, 50 μl of 2.12 nM 3H-N-methylscopolamine radioligand in compound dilution buffer was added. The total volume in each well was 200 μl. The final concentration of Methoctramine is 2 μM. The filter plate was pre-blocked using 0.3% PEI for at least 15 minutes, and then washed twice with 200 μl PBS. The assay plate is incubated for 1 hour at room temperature with gentle shaking. The contents of the assay plate are then transferred to the filter plate, and washed three times using 200 μl PBS. About 40 μl of scint is added to each well and then the plate is allowed to sit at room temperature for 18h, and then counted using a Packard Topcount NXT. Counting was typically performed for 1minute per well using a standard protocol on the Packard counter, and the data was fit to the four parameter equation described in Example 19.

A similar procedure was used to measure binding at bladder M_2, but in this case, 2 μM Darifenacin was used to block >99% of the M_2 receptor, but minimal M_3 receptor.

Example 22

Ex Vivo Rat Bladder Contraction Assay

The ability of the test compound to inhibit cholinergically stimulated bladder contraction was tested as follows:

Male Sprague-Dawley rats weighing 250 – 300 g are killed by CO_2 overdose. The bladder was removed and placed in a petri dish containing Krebs-Henseleit solution at room temperature. The apex and dome areas of the bladder were discarded and the remaining tissue cut into longitudinal strips (4 from each rat). The strips were mounted in an organ bath containing Krebs-Henseleit solution at 37

^0C, under a resting tension of 0.5g. The tissues were allowed to equilibrate for 60mins. (washes at 0, 30 and 60mins). Tension was readjusted to 1g as necessary. A cumulative concentration response curve to carbachol (10-8M to 10-5M (e.g.) in 3-fold increments) was constructed in each tissue. Tissues were then washed every 5min. for 30min. and tension readjusted to 1g. A further 30min. later, muscarinic antagonist (typically 1x10-7M) or vehicle was added. 30min. after antagonist or vehicle addition, a cumulative concentration response curve to carbachol (10-8M to 10-3M (e.g.)) was constructed. Data from each concentration response curve was expressed as a percentage of the maximum contraction to carbachol. The EC50 values were calculated. The concentration-ratios were calculated taking into account any spontaneous shift in the control tissue. For competitive antagonists, the pKb value was calculated using the following equation:

$$pKb = -\log \frac{[\text{antagonist concentration}]}{CR-1}$$

Example 23

In Vivo Rat Salivation Assay

Male Sprague-Dawley rats weighing 250 – 300 g were anesthetized with pentobarbital (60mg/kg i.p.). Rats were placed on a heated blanket under a 20 degree incline. A swab was placed in the rat's mouth. Muscarinic antagonist or vehicle was administered i.v. via the tail vein. 5 min. later, oxotremorine (0.3mg/kg) was administered s.c.. The swab was discarded and replaced by a pre-weighed swab. Saliva was then collected for 15min. After 15min., the swab was weighed and the difference in its weight was used to calculate the antisecretory potency of the antagonists. The ID50 value for each antagonist is calculated using the four parameter fit equation given above.

Example 24

In Vivo Bladder Assay

Male Sprague-Dawley rats weighing 250 – 300 g were anesthetized with urethane (1.3 g/kg, i.p.), inactin (25 mg/kg, i.p.), and xylazine (4 mg, i.p.). The jugular (or femoral) vein was Isolate and ligated and a small incision was made in the vein distal to the ligation. A catheter (micro-Renathane tubing (0.014 mm ID x 0.033 mm OD) was filled with saline was nserted into the vein and secured into place with suture thread. The trachea was isolated and place da small hole between two of the rings. Tubing (1.57 mm ID x 2.08 mm OD) was inserted into the trachea and tied into place with suture thread. The incision was closed leaving the tubing exposed. The tracheotomy was to prevent the animal from asphyxiating on his own saliva following oxotremorine administration. The stomach was shaved and then cleaned with ethanol. A midline sagital incision was made in the skin and muscle layers of the lower stomach. The bladder was exposed and the saline filled cannula (22-gauge needle attached to a pressure transducer with PE 90 tubing) was inserted into the apex of the bladder to the most distal part of the bladder. The bladder was placed back into the peritoneal cavity. The bladder was emptied manually by disconnecting the cannula and allowing the contents to flow out until the bladder was approximately 1 cm in diameter. The incision was closed with suture thread, first the muscle layer, then the skin in order to keep the bladder moist and warm. The exposed portion of the cannula to the skin surface was sutured to hold it in place. After 15 min. oxotremorine (0.3 mg/kg, SC, baseweight) was injected. After 10 min. (or until baseline stabilizes) a test compound or a reference standard was injected with a dose equivalent to 0.005 – 0.01 mg/kg, IV, baseweight of atropine that produces a 30-70% decrease in intraluminal pressure. After 5 min. a high dose of atropine 0.1 mg/kg was injected, IV to establish the true 100% inhibition point.

For data analyses, first determine oxotremorine response (zero inhibition) by measuring the mean pressure 1 minute prior to the antagonist injection. Then, to assess antagonist inhibition, measure the mean pressure beginning 1 minute and ending 2 minutes after antagonist administration. If the pressure has not leveled off

after 1 minute, wait until it is stable and then take a 1-minute sample of the mean. Lastly, to determine the true 100% inhibition point, measure the mean pressure beginning 1 minutes and ending 2 minutes after the high dose atropine challenge. The percent inhibition by the antagonist can be determined by the ratio of the decrease from the zero to 100% values.

The formula is: oxotremorine mean – treatment mean *100

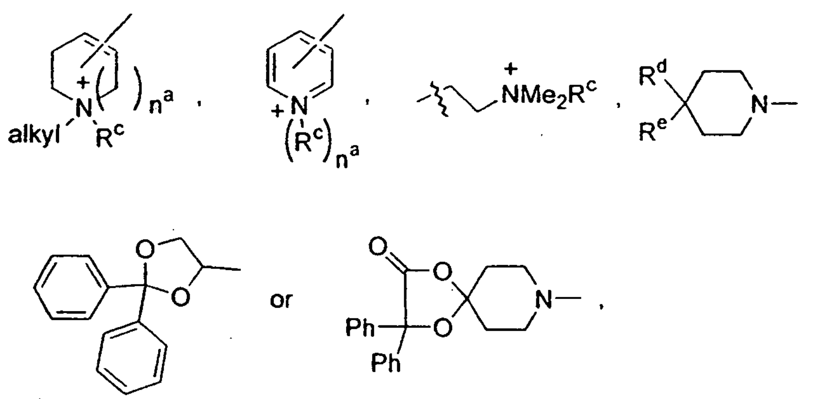
oxotremorine mean – atropine mean.

The foregoing invention has been described in some detail by way of illustration and example, for purposes of clarity and understanding. It will be obvious to one of skill in the art that changes and modifications may be practiced within the scope of the appended claims. Therefore, it is to be understood that the above description is intended to be illustrative and not restrictive. The scope of the invention should, therefore, be determined not with reference to the above description, but should instead be determined with reference to the following appended claims, along with the full scope of equivalents to which such claims are entitled.

All patents, patent applications and publications cited in this application are hereby incorporated by reference in their entirety for all purposes to the same extent as if each individual patent, patent application or publication were so individually denoted.

WHAT IS CLAIMED IS:

1. A multibinding compound comprising from 2 to 10 ligands covalently attached to one or more linkers, wherein each of said ligands comprises, independently of each other, a muscarinic receptor antagonist or an allosteric modulator of a muscarinic receptor and pharmaceutically acceptable salts thereof, provided that at least one of said ligands is a muscarinic receptor antagonist, and further provided that when the multibinding compound comprises of 2 or 3 ligands, then only one of the ligands.is 11-acetyl-5,11-dihydro-6H-pyrido[2,3b][1,4]-benzodiazepin-6-one, N-methylquiniclidine, or a compound of formula:



wherein:

n^a is 0 or 1;

R^c is hydrogen or alkyl;

R^d is hydrogen; and

R^e is $-CO_2CR^f(phenyl)_2$ wherein R^f is hydrogen or hydroxy.

2. A multibinding compound of Formula (I):

$$(L)_p(X)_q \tag{I}$$

wherein:

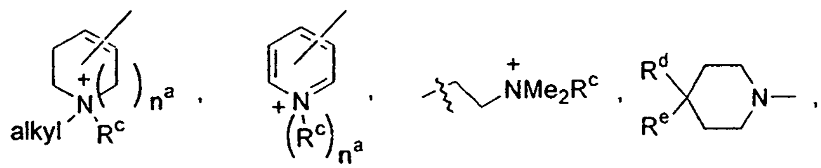
each L is, independently of each other, a muscarinic receptor antagonist or an

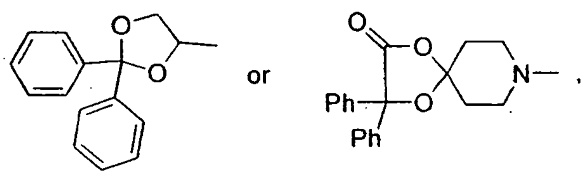
allosteric modulator of a muscarinic receptor;

each X is independently a linker;

p is an integer of from 2 to 10; and

q is an integer of from 1 to 20, and pharmaceutically acceptable salts thereof, provided that at least one of said ligands is a muscarinic receptor antagonist, and further provided that when the multibinding compound comprises of 2 or 3 ligands, then only one of the ligands.is 11-acetyl-5,11-dihydro-6H-pyrido[2,3][1,4]benzodiazepin-6-one, N-methylquiniclidine, or a compound of formula:





wherein:

n^a is 0 or 1;

R^c is hydrogen or alkyl;

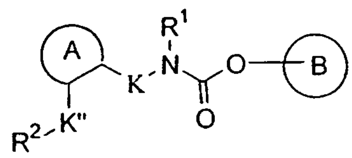
R^d is hydrogen; and

R^e is $-CO_2CR^f(phenyl)_2$ wherein R^f is hydrogen or hydroxy.

3. The multibinding compound of Claim 2 wherein *q* is less than *p*.

4. The multibinding compound of Claim 3 wherein each ligand, L, that is a muscarinic receptor antagonist in the multibinding compound of Formula (I) is independently selected from a group consisting of:

(1) a compound of formula (a):



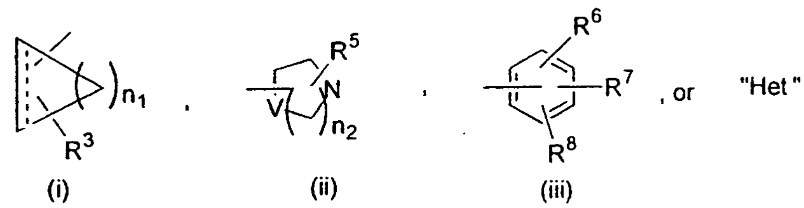
(a)

wherein:

A is an aryl or a heteroaryl ring;

R^1 is hydrogen or alkyl;

R^2 is selected from a group consisting of formula (i), (ii), (iii), or "Het":



wherein:

----- is an optional double bond;

n_1 is an integer of from 1 to 4;

n_2 is an integer of from 1 to 3;

V is -CH-, -O-, -S(O)n_3- (where n_3 is an integer of from 0 to 2), or -NR^4- (wherein R^4 is hydrogen, alkyl, substituted alkyl, aryl, or heteroaryl);

"Het" is a heteroaryl ring which optionally attaches the ligand to a linker;

R^3 is hydrogen, alkyl, amino, substituted amino, -OR^a (where R^a is hydrogen, alkyl, or acyl), or a covalent bond attaching the ligand to a linker;

R^5 is hydrogen, alkyl, amino, substituted amino, -OR^b (where R^b is hydrogen or alkyl), aryl, aralkyl, heteroaralkyl, or a covalent bond attaching the ligand to a linker;

R^6, R^7, and R^8 are, independently of each other, hydrogen, halo, hydroxy, alkoxy, haloalkoxy, carboxy, alkoxycarbonyl, alkyl optionally substituted with one, two or three substituents selected from halo, hydroxy, carboxy, alkoxycarbonyl, alkylthio, alkylsulfonyl, amino, or substituted amino, or a covalent bond attaching

the ligand to a linker;

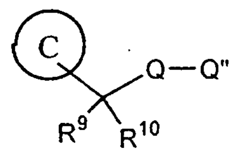
K is a bond or an alkylene group;

K" is a bond, -C(O)-, -S(O)$_{n4}$- (where n_4 is an integer of from 0 to 2), or an alkylene group optionally substituted with a hydroxyl group; and

B is a heterocycloamino group which optionally attaches the ligand to a linker;

provided that at least one of the R^5, R^6, R^7, R^8, "Het", or the heterocycloamino group attaches the ligand to a linker;

(2) a compound of formula (b):



(b)

wherein:

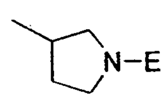
C is an aryl or heteroaryl ring which optionally attaches the ligand to a linker;

R^9 is hydrogen, hydroxy, cyano, aminocarbonyl, alkyl optionally substituted with one, two or three substituents selected from halo, hydroxy, carboxy, alkoxycarbonyl, alkylthio, alkylsulfonyl, amino, substituted amino, or a covalent bond attaching the ligand to a linker;

R^{10} is hydrogen, aryl, heteroaryl, alkyl optionally substituted with one, two or three substituents selected from halo, hydroxy, carboxy, alkoxycarbonyl, alkylthio, alkylsulfonyl, amino, substituted amino, or a covalent bond attaching the ligand to a linker;

Q is a single bond or -C(O)O- such that:

when Q is a bond then, Q" is a group of formula (iv):

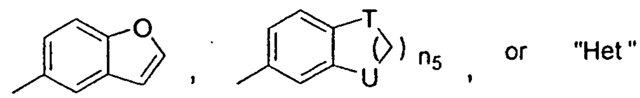


(iv)

where:

E is hydrogen, a covalent bond attaching the ligand to a linker, or $-CH_2-W-R^{11}$ wherein W is a single bond or alkylene wherein one of the carbon atoms may optionally be replaced by -O-, -S-, or $-NR^g-$ (wherein R^g is hydrogen or alkyl); and

R^{11} is a group of formula (v), (vi), or "Het":



(v) (vi)

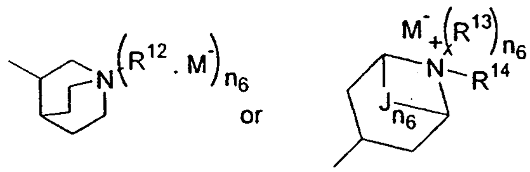
wherein:

T and U are, independently of each other, -O- or $-CH_2-$;

n_5 is an integer of from 1 to 3; and

"Het" is heteroaryl provided that at least one of C, E, R^9, and R^{10} attaches the ligand to a linker; and

when Q is -C(O)O- or -NHC(O)O- then, Q" is a group of formula (vii) or (viii):



(vii) (viii)

wherein:

n_6 is 0 or 1;

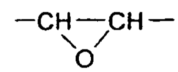
M^- is a counterion;

R^{12} is a covalent bond attaching the ligand to a linker;

R^{13} is alkyl, alkenyl, cycloalkyl, or a covalent bond attaching the ligand to a linker;

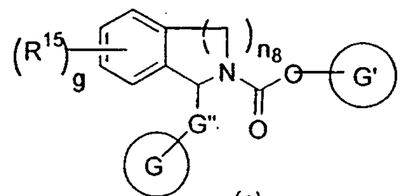
R^{14} is hydrogen, alkyl, or a covalent bond attaching the ligand to a linker; and

J is:

$-(CH_2)_2-$, $-(CH_2)_3-$, or 

provided that at least one of the C, R^9, R^{10}, R^{12}, R^{13}, and R^{14} attaches the ligand to a linker;

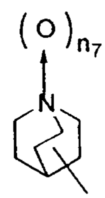
(3) a compound of formula (c):



(c)

wherein:

G' is pyrrolidine, piperidine, or



which optionally attach the ligand to a linker;

n_7 is an 0 or 1, provided that when the nitrogen atom of the quinclidine ring attaches the ligand to the linker then n_7 is 0;

n_8 is 1 or 2;

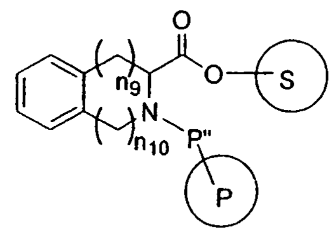
g is an integer of from 0 to 3;

each R^{15} is, independently of each other, hydrogen, halogen, nitro, cyano, hydroxy, alkoxy, carboxy, alkoxycarbonyl, acyl, thio, alkylthio, alkylsulfonyl, alkylsulfinyl, sulfonamido, alkylsulfonamido, carbamoyl, thiocarbamoyl, mono or dialkylcarbamoyl, amino, mono- or dialkylamino, methylenedioxy, ethylenedioxy, alkyl optionally substituted with one, two or three substituents selected from halo, hydroxy, carboxy, alkoxycarbonyl, alkylthio, alkylsulfonyl, amino, or substituted amino, or a covalent bond attaching the ligand to a linker;

G is aryl, heteroaryl, heterocyclyl, or cycloalkyl which optionally attach the ligand to a linker; and

G" is a single bond or an alkylene group provided that at least one of the R^{15}, G, and G" attaches the ligand to a linker;

(4) a compound of formula (d):



(d)

wherein:

n_9 is 1 or 2;

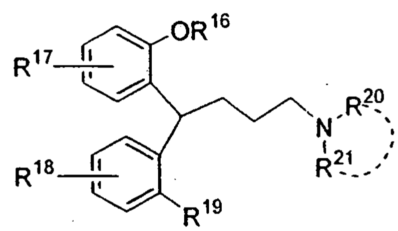
n_{10} is 0 or 1 provided that n_9+n_{10} are 1 or 2;

P is an aryl or heteroaryl ring which optionally attaches the ligand to a linker;

P" is a single bond or an alkylene group;

S is a heterocycloamino ring which optionally attaches the ligand to a linker provided that at least one of the P and S attaches the ligand to a linker;

(5) a compound of formula (e):



(e)

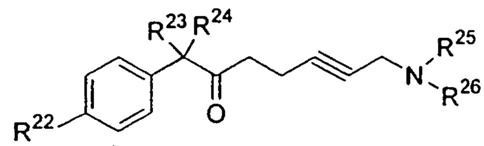
wherein:

R^{16} is hydrogen, alkyl, or a covalent bond attaching the ligand to a linker;

R^{17}, R^{18}, and R^{19} are, independently of each other, hydrogen, alkyl, alkoxy, hydroxy, carbamoyl, sulfanoyl, halo, or a covalent bond attaching the ligand to a linker;

R^{20} and R^{21} are, indepenaently of each other, hydrogen, alkyl or a covalent bond attaching the ligand to a linker; or R^{20} and R^{21} together with the nitrogen atom to which they are attached form a heterocycloamino ring which optionally attaches the ligand to a linker provided that at least one of the R^{16}, R^{17}, R^{18}, R^{19}, R^{20}, and R^{21} attaches the ligand to a linker; or

(6) a compound of formula (f):



(f)

wherein:

R^{22} is hydrogen or halo;

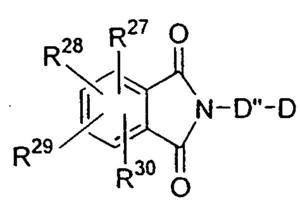
R^{23} is alkyl, cycloalkyl, aryl, heteroaryl, heterocyclyl, or heterocyclylalkyl;

R^{24} is hydroxy, halo, or a covalent bond attaching the ligand to a linker;

R^{25} and R^{26} are, independently of each other, hydrogen, alkyl, aralkyl, or a covalent bond attaching the ligand to a linker, or R^{25} and R^{26} together with the nitrogen atom to which they are attached form a heterocycloamino group which optionally attaches the ligand to a linker provided that at least one of the R^{24}, R^{25}, and R^{26} attaches the ligand to a linker.

5. The multibinding compound of Claim 4 wherein each ligand, L, that is a allosteric modulator of a muscarinic receptor in the multibinding compound of Formula (I) is independently selected from a group consisting of:

(1) a compound of formula (g):



(g)

wherein:

D" is alkylene;

D is $-NR^{31}R^{32}$, $-N^{+}(R^{33}R^{34}R^{35})$ or $-OR^{32}$ where R^{31}, R^{33}, and R^{34} are, independently of each other, hydrogen, alkyl, or aralkyl; and R^{32} and R^{35} represent a covalent bond attaching the ligand to a linker;

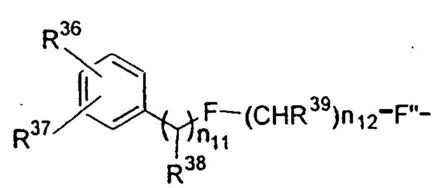
R^{27} is hydrogen, halo, nitro, cyano, hydroxy, alkoxy, carboxy, alkoxycarbonyl, acyl, thio, alkylthio, alkylsulfonyl, alkylsulfinyl, sulfonamido, alkylsulfonamido, carbamoyl, thiocarbamoyl, mono or dialkylcarbamoyl, amino, mono- or dialkylamino, aryl, aryloxy, arylthio, heteroaryl, heteraryloxy, heteroarylthio, heterocyclyl, heterocyclyloxy, aralkyl, heteroaralkyl, or alkyl optionally substituted with one, two or three substituents selected from halo, hydroxy, carboxy, alkoxycarbonyl, alkylthio, alkylsulfonyl, amino, or substituted amino;

R^{28} is hydrogen, halo, nitro, cyano, hydroxy, alkoxy, carboxy, alkoxycarbonyl, acyl, thio, alkylthio, alkylsulfonyl, alkylsulfinyl, sulfonamido, alkylsulfonamido, carbamoyl, thiocarbamoyl, mono or dialkylcarbamoyl, amino, mono- or dialkylamino, or alkyl optionally substituted with one, two, or three substituents selected from halo, hydroxy, carboxy, alkoxycarbonyl, alkylthio, alkylsulfonyl, amino, or substituted amino;

R^{29} and R^{30} are, independently of each other, hydrogen, alkyl, haloalkyl, halo, nitro, cyano, hydroxy, alkoxy, alkoxycarbonyl, acyl, thio, alkylthio, amino, mono- or dialkylamino; or

one of R^{27}, R^{28}, R^{29}, or R^{30} together with the adjacent group forms a methylenedioxy or ethylenedioxy group; or

(2) a compound of formula (h):



(h)

wherein:

n_{11} is an integer of from 1 to 7;

n_{12} is an integer of from 0 to 7;

F is $-NR^{40}-$, -O-, -S-, or $-CHR^{41}-$ (wherein R^{40} and R^{41} are, independently of each other, hydrogen or alkyl);

F" is a covalent bond, $-OR^{43}$, $-NR^{42}R^{43}$, or $-N^{+}R^{43}R^{44}R^{45}$ wherein R^{42} is hydrogen or alkyl, R^{44} and R^{45} are alkyl, and R^{43} is a covalent bond attaching the ligand to a linker;

R^{36} is hydrogen, halo, nitro, cyano, hydroxy, alkoxy, carboxy, alkoxycarbonyl, acyl, thio, alkylthio, alkylsulfonyl, alkylsulfinyl, sulfonamido, alkylsulfonamido, carbamoyl, thiocarbamoyl, mono or dialkylcarbamoyl, amino, mono- or dialkylamino, aryl, aryloxy, arylthio, heteroaryl, heteraryloxy, heteroarylthio, heterocyclyl, heterocyclyloxy, aralkyl, heteroaralkyl, or alkyl optionally substituted with one, two or three substituents selected from halo, hydroxy, carboxy, alkoxycarbonyl, alkylthio, alkylsulfonyl, amino, or substituted amino;

R^{37} is hydrogen, halo, nitro, cyano, hydroxy, alkoxy, alkoxycarbonyl, acyl, thio, alkylthio, amino, mono- or dialkylamino, aryl, aryloxy, arylthio, heteroaryl, heteraryloxy, heteroarylthio, heterocyclyl, heterocyclyloxy, aralkyl, heteroaralkyl, or alkyl optionally substituted with one, two or three substituents selected from halo, hydroxy, carboxy, alkoxycarbonyl, alkylthio, alkylsulfonyl, amino, or substituted amino; and

R^{38} is hydrogen, alkyl, halo, hydroxy, alkoxy, or a covalent bond attaching the ligand to a linker provided that at least one of R^{38} and R^{43} attaches the ligand to a linker.

6. The multibinding compound of Claim 5 wherein each linker independently has the formula:

$$-X^{a}-Z-(Y^{a}-Z)_{m}-Y^{b}-Z-X^{a}-$$

wherein

m is an integer of from 0 to 20;

X^a at each separate occurrence is selected from the group consisting of -O-, -S-, -NR-, -C(O)-, -C(O)O-, -C(O)NR-, -C(S), -C(S)O-, -C(S)NR- or a covalent bond where R is as defined below;

Z is at each separate occurrence is selected from the group consisting of alkylene, substituted alkylene, cycloalkylene, substituted cylcoalkylene, alkenylene, substituted alkenylene, alkynylene, substituted alkynylene, cycloalkenylene, substituted cycloalkenylene, arylene, heteroarylene, heterocyclene, or a covalent bond;

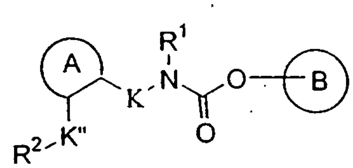
Y^a and Y^b at each separate occurrence are selected from the group consisting of -O-, -C(O)-, -OC(O)-, -C(O)O-, -NR-, -S(O)n-, -C(O)NR'-, -NR' C(O)-, -NR' C(O)NR'-, -NR' C(S)NR'-, -C(=NR')-NR'-, -NR'-C(=NR')-, -OC(O)-NR'-, -NR'-C(O)-O-, -N=C(X^a)-NR'-, -NR'-C(X^a)=N-,-P(O)(OR')-O-, -O-P(O)(OR')-, -S$(O)_n$CR' R"-, -S$(O)_n$-NR'-, -NR'-S$(O)_n$-, -S-S-, and a covalent bond; where *n* is 0, 1 or 2; and R, R' and R" at each separate occurrence are selected from the group consisting of hydrogen, alkyl, substituted alkyl, cycloalkyl, substituted cycloalkyl, alkenyl, substituted alkenyl, cycloalkenyl, substituted cycloalkenyl, alkynyl, substituted alkynyl, aryl, heteroaryl and heterocyclic.

7. The multibinding compound of Claim 6 wherein p is 2 and q is 1.

8. The multibinding compound of Claim 7 wherein both the ligands are muscarinic receptor antagonists.

9. The multibinding compound of Claim 8 wherein the ligands are selected from a group consisting of:

(1) a compound of formula (a):



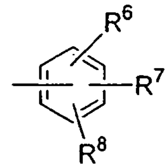
(a)

wherein:

A is a phenyl;

R^1 is hydrogen;

R^2 is a group of formula (iii):



(iii)

wherein:

R^6, R^7, and R^8 are, independently of each other, hydrogen, alkyl, nitro, hydroxy, or amino, or a covalent bond attaching the ligand to a linker;

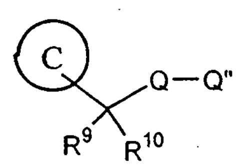
K and K" are a single bond; and

B is either:

(i) pyrrolidine, piperidine, or hexahydroazepine which optionally attach the ligand to a linker; or

(ii) quinuclidine, 1-azabicyclo[2.2.1]heptyl, or 1-azabicyclo[3.2.1]octyl optionally atttach the ligand to a linker wherein a bridge head carbon atom or a carbon atom adjacent thereto is the binding position with the oxygen atom;

(2) a compound of formula (b):



(b)

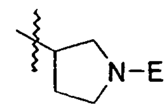
wherein:

when Q is a single bond then:

C and R^{10} are a phenyl ring;

R^9 is aminocarbonyl, or a covalent bond attaching the ligand to a linker; and

Q" is a group of formula (iv):

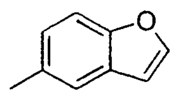


(iv)

where:

E is hydrogen, a covalent bond attaching the ligand to a linker, or $-CH_2-W-R^{11}$ wherein W is $-(CH_2)_2-$ or $-(CH_2)_3-$ and

R^{11} is a group of formula (v):



(v)

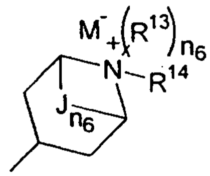
and

when Q is -NHC(O)O- then:

R^9 is hydrogen;

C and R^{10} are phenyl; and

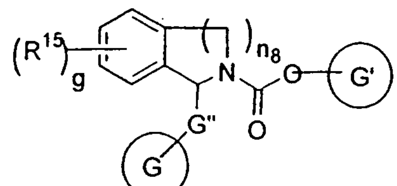
Q" is a group of formula (viii):



(viii)

wherein n_6 is 0 and R^{14} is hydrogen, alkyl, or a covalent bond attaching the ligand to a linker;

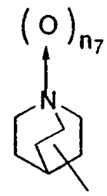
(3) a compound of formula (c):



(c)

wherein:

G' is pyrrolidine, piperidine, or



which optionally attach the ligand to a linker;

n_7 is an 0 or 1 provided that when the nitrogen atom of the quinclidine ring attaches the ligand to a linker then n_7 is 0;

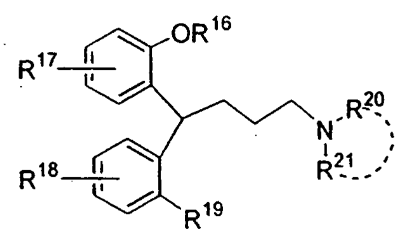
n_8 is 2;

g is 0;

G is phenyl which optionally link the ligand to a linker; and

G" is a single bond;

(4) a compound of formula (e):



e)

wherein:

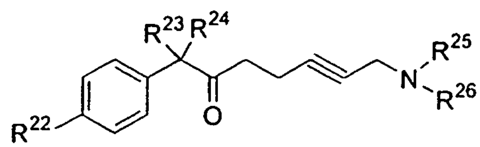
R^{16} is methyl or a covalent bond linking the ligand to a linker;

R^{17} is either meta or para to the -OR^{16} group and is hydrogen, hydroxy, methyl or a covalent bond linking the ligand to a linker;

R^{18} an R^{19} are hydrogen; and

R^{20} and R^{21} are, independently of each other, N,N-(isopropyl)amino, N-methyl-N-*tert*-butylamino, or one of R^{20} and R^{21} is hydrogen, methyl, or ethyl and the other is a covalent bond attaching the ligand to a linker; or

(5) a compound of formula (f):



(f)

wherein:

R^{22} is hydrogen;

R^{23} is cyclohexyl;

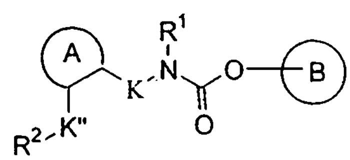
R^{24} is hydroxy or a covalent bond attaching the ligand to a linker;

R^{25} and R^{26} are, independently of each other, hydrogen, methyl, ethyl, or a covalent bond attaching the ligand to a linker.

10. The multibinding compound of Claim 7 wherein one of the ligands is a muscarinic receptor antagonist and the other is a modulator of a muscarinic receptor.

11. The multibinding compound of Claim 10 wherein the ligand that is a muscarinic receptor antagonist is selected from the group consisting of:

(1) a compound of formula (a):



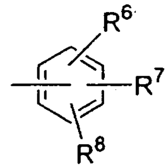
(a)

wherein:

A is a phenyl;

R^1 is hydrogen;

R^2 is a group of formula (iii):



(iii)

wherein:

R^6, R^7, and R^8 are, independently of each other, hydrogen, alkyl, nitro, hydroxy, or amino, or a covalent bond attaching the ligand to a linker;

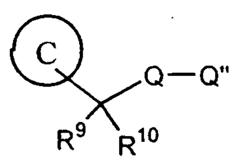
K and K" are a single bond; and

B is either:

(i) pyrrolidine, piperidine, or hexahydroazepine optionally attaching the ligand to a linker; or

(ii) quinuclidine, 1-azabicyclo[2.2.1]heptyl, or 1-azabicyclo[3.2.1]octyl optionally atttaching the ligand to a linker wherein a bridge head carbon atom or a carbon atom adjacent thereto is the binding position with the oxygen atom;

(2) a compound of formula (b):



(b)

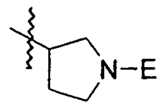
wherein:

when Q is a single bond then:

C and R^{10} are a phenyl ring;

R^9 is aminocarbonyl, or a covalent bond attaching the ligand to a linker; and

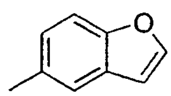
Q" is a group of formula (iv):



(iv)

where:

E is hydrogen, a covalent bond attaching the ligand to a linker, or $-CH_2-W-R^{11}$ wherein W is $-(CH_2)_2-$ or $-(CH_2)_3-$, and R^{11} is a group of formula (v):



(v)

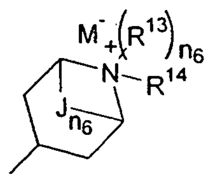
and

when Q is -NHC(O)O- then:

R^9 is hydrogen;

C and R^{10} are phenyl; and

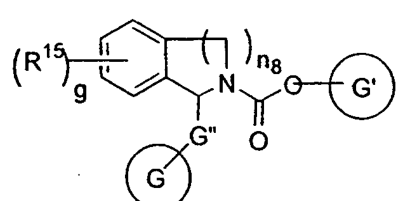
Q" is a group of formula (viii):



(viii)

wherein n_6 is 0 and R^{14} is hydrogen, alkyl, or a covalent bond attaching the ligand to a linker;

(3) a compound of formula (c):



(c)

wherein:

G' is pyrrolidine, piperidine, or

which optionally attach the ligand to a linker;

n_7 is an 0 or 1 provided that when the nitrogen atom of the quinclidine ring attaches the ligand to a linker then n_7 is 0;

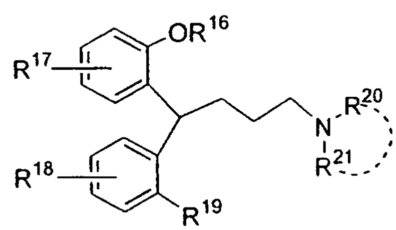
n_8 is 2;

g is 0;

G is phenyl which optionally link the ligand to a linker; and

G" is a single bond;

(4) a compound of formula (e):



(e)

wherein:

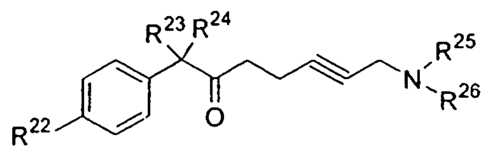
R^{16} is methyl or a covalent bond linking the ligand to a linker;

R^{17} is either meta or para to the -OR^{16} group and is hydrogen, hydroxy, methyl, or a covalent bond linking the ligand to a linker;

R^{18} an R^{19} are hydrogen; and

R^{20} and R^{21} are, independently of each other, N,N-(isopropyl)amino, N-methyl-N-*tert*-butylamino, or one of R^{20} and R^{21} is hydrogen, methyl, or ethyl and the other is a covalent bond attaching the ligand to a linker; or

(5) a compound of formula (f):



(f)

wherein:

R^{22} is hydrogen;

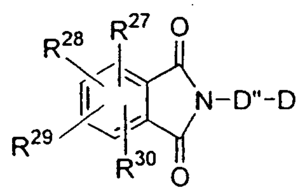
R^{23} is cyclohexyl;

R^{24} is hydroxy or a covalent bond attaching the ligand to a linker;

R^{25} and R^{26} are, independently of each other, hydrogen, methyl, ethyl, or a covalent bond attaching the ligand to a linker; and

the modulator of a muscarinic receptor is selected from a group consisting of:

(5) a compound of formula (g):



(g)

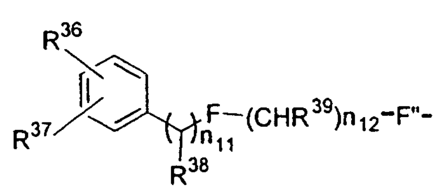
wherein:

D" is $-(CH_2)n_{43}-$ where n_{43} is an integer of from 2-8;

D is $-NR^{31}R^{32}$, $-N^{+}(R^{33}R^{34}R^{35})M^{-}$ or $-OR^{32}$ where R^{31}, R^{33}, and R^{34} are, independently of each other, hydrogen or methyl, and R^{32} and R^{35} represent a covalent bond attaching the ligand to a linker;

R^{27}, R^{28}, R^{29}, and R^{30} are hydrogen; and

(6) a compound of formula (h):



(h)

wherein:

n_{11} is an integer of from 1 to 7;

n_{12} is an integer of from 0to 7;

R^{36} and R^{38} are hydrogen.

R^{37} is ortho to the -(CHR^{38})- group and is hydrogen or methoxy;

F is -O-, -NH-, or -N(CH_3)-;

F" is a covalent bond, methylamino, or dimethylamino wherein the nitrogen atom is attached to a linker.

12. A pharmaceutical composition comprising a pharmaceutically acceptable carrier and an effective amount of a multibinding compound of Formula (I):

$$(L)_p(X)_q$$

(I)

wherein:

each L is, independently of each other, a muscarinic receptor antagonist or an allosteric modulator of a muscarinic receptor;

each X is independently a linker;

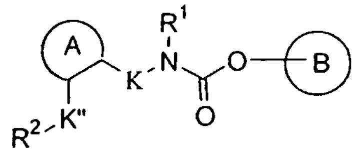
p is an integer of from 2 to 10; and

q is an integer of from 1 to 20, and pharmaceutically acceptable salts thereof provided that at least one of said ligands is a muscarinic receptor antagonist.

13. The pharmaceutical composition of Claim 12 wherein *q* is less than *p*.

14. The pharmaceutical composition of Claim 13 wherein each ligand that is a muscarinic receptor antagonist is independently selected from the group consisting of:

(1) a compound of formula (a):



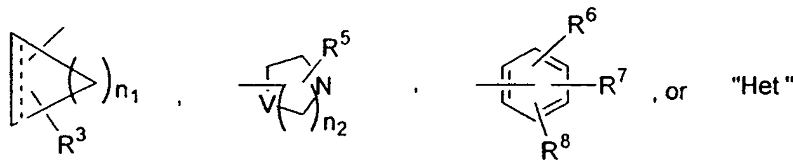
(a)

wherein:

A is an aryl or a heteroaryl ring;

R^1 is hydrogen or alkyl;

R^2 is selected from a group consisting of formula (i), (ii), (iii), or "Het":



wherein:

----- is an optional double bond;

n_1 is an integer of from 1 to 4;

n_2 is an integer of from 1 to 3;

V is -CH-, -O-, -S(O)n_3- (where n_3 is an integer of from 0 to 2), or -NR^4- (wherein R^4 is hydrogen, alkyl, substituted alkyl, aryl, or heteroaryl);

"Het" is a heteroaryl ring which optionally attaches the ligand to a linker;

R^3 is hydrogen, alkyl, amino, substituted amino, -OR^a (where R^a is hydrogen, alkyl, or acyl), or a covalent bond attaching the ligand to a linker;

R^5 is hydrogen, alkyl, amino, substituted amino, -OR^b (where R^b is hydrogen or alkyl), aryl, aralkyl, heteroaralkyl, or a covalent bond attaching the ligand to a linker;

R^6, R^7, and R^8 are, independently of each other, hydrogen, halo, hydroxy, alkoxy, haloalkoxy, carboxy, alkoxycarbonyl, alkyl optionally substituted with one, two or three substituents selected from halo, hydroxy, carboxy, alkoxycarbonyl,

alkylthio, alkylsulfonyl, amino, or substituted amino, or a covalent bond attaching the ligand to a linker;

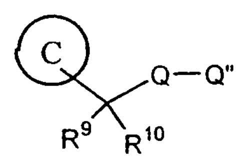
K is a bond or an alkylene group;

K" is a bond, -C(O)-, $-S(O)_{n4}-$ (where n_4 is an integer of from 0 to 2), or an alkylene group optionally substituted with a hydroxyl group; and

B is a heterocycloamino group which optionally attaches the ligand to a linker;

provided that at least one of the R^5, R^6, R^7, R^8, "Het", or the heterocycloamino group attaches the ligand to a linker;

(2) a compound of formula (b):



(b)

wherein:

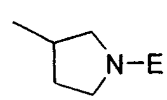
C is an aryl or heteroaryl ring which optionally attaches the ligand to a linker;

R^9 is hydrogen, hydroxy, cyano, aminocarbonyl, alkyl optionally substituted with one, two or three substituents selected from halo, hydroxy, carboxy, alkoxycarbonyl, alkylthio, alkylsulfonyl, amino, substituted amino, or a covalent bond attaching the ligand to a linker;

R^{10} is hydrogen, aryl, heteroaryl, alkyl optionally substituted with one, two or three substituents selected from halo, hydroxy, carboxy, alkoxycarbonyl, alkylthio, alkylsulfonyl, amino, substituted amino, or a covalent bond attaching the ligand to a linker;

Q is a single bond or -C(O)O- such that:

when Q is a bond then, Q" is a group of formula (iv):

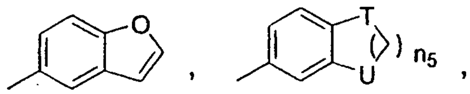


(iv)

where:

E is hydrogen, a covalent bond attaching the ligand to a linker, or $-CH_2-W-R^{11}$ wherein W is a single bond or alkylene wherein one of the carbon atoms may optionally be replaced by -O-, -S-, or $-NR^g-$ (wherein R^g is hydrogen or alkyl); and

R^{11} is a group of formula (v), (vi), or "Het":



(v) (vi)

or "Het"

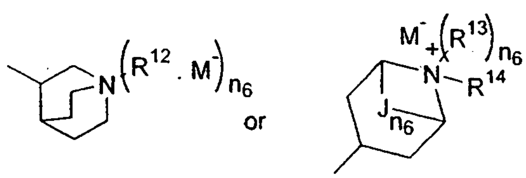
wherein:

T and U are, independently of each other, -O- or $-CH_2-$;

n_5 is an integer of from 1 to 3; and

"Het" is heteroaryl provided that at least one of C, E, R^9, and R^{10} attaches the ligand to a linker; and

when Q is -C(O)O- or -NHC(O)O- then, Q" is a group of formula (vii) or (viii):



(vii) or (viii)

wherein:

n_6 is 0 or 1;

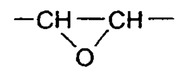
M^- is a counterion;

R^{12} is a covalent bond attaching the ligand to a linker;

R^{13} is alkyl, alkenyl, cycloalkyl, or a covalent bond attaching the ligand to a linker;

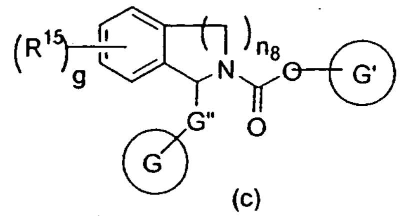
R^{14} is hydrogen, alkyl, or a covalent bond attaching the ligand to a linker; and

J is:

$-(CH_2)_2-$, $-(CH_2)_3-$, or 

provided that at least one of the C, R^9, R^{10}, R^{12}, R^{13}, and R^{14} attaches the ligand to a linker;

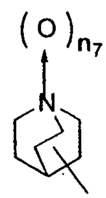
(3) a compound of formula (c):



(c)

wherein:

G' is pyrrolidine, piperidine, or



which optionally attach the ligand to a linker;

n_7 is an 0 or 1, provided that when the nitrogen atom of the quinclidine ring attaches the ligand to the linker then n_7 is 0;

n_8 is 1 or 2;

g is an integer of from 0 to 3;

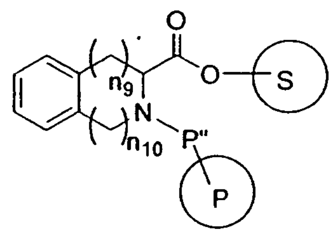
each R^{15} is, independently of each other, hydrogen, halogen, nitro, cyano, hydroxy, alkoxy, carboxy, alkoxycarbonyl, acyl, thio, alkylthio, alkylsulfonyl, alkylsulfinyl, sulfonamido, alkylsulfonamido, carbamoyl, thiocarbamoyl, mono or dialkylcarbamoyl, amino, mono- or dialkylamino, methylenedioxy, ethylenedioxy, alkyl optionally substituted with one, two or three substituents selected from halo, hydroxy, carboxy, alkoxycarbonyl, alkylthio, alkylsulfonyl, amino, or substituted amino, or a covalent bond attaching the ligand to a linker;

G is aryl, heteroaryl, heterocyclyl, or cycloalkyl which optionally attach the

ligand to a linker; and

G" is a single bond or an alkylene group provided that at least one of the R^{15}, G, and G" attaches the ligand to a linker;

(4) a compound of formula (d):



(d)

wherein:

n_9 is 1 or 2;

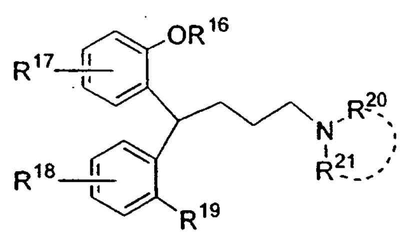
n_{10} is 0 or 1 provided that n_9+n_{10} are 1 or 2;

P is an aryl or heteroaryl ring which optionally attaches the ligand to a linker;

P" is a single bond or an alkylene group;

S is a heterocycloamino ring which optionally attaches the ligand to a linker provided that at least one of the P and S attaches the ligand to a linker;

(5) a compound of formula (e):



(e)

wherein:

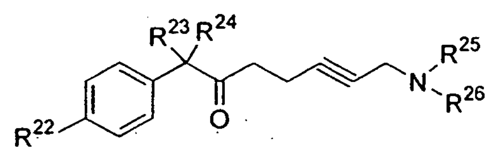
R^{16} is hydrogen, alkyl, or a covalent bond attaching the ligand to a linker;

R^{17}, R^{18}, and R^{19} are, independently of each other, hydrogen, alkyl, alkoxy, hydroxy, carbamoyl, sulfanoyl, halo, or a covalent bond attaching the ligand to a linker;

R^{20} and R^{21} are, independently of each other, hydrogen, alkyl or a covalent

bond attaching the ligand to a linker; or R^{20} and R^{21} together with the nitrogen atom to which they are attached form a heterocycloamino ring which optionally attaches the ligand to a linker provided that at least one of the R^{16}, R^{17}, R^{18}, R^{19}, R^{20}, and R^{21} attaches the ligand to a linker; or

(6) a compound of formula (f):



(f)

wherein:

R^{22} is hydrogen or halo;

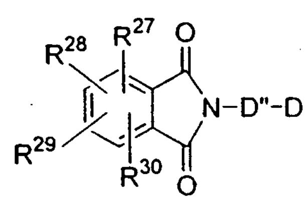
R^{23} is alkyl, cycloalkyl, aryl, heteroaryl, heterocyclyl, or heterocyclylalkyl;

R^{24} is hydroxy, halo, or a covalent bond attaching the ligand to a linker;

R^{25} and R^{26} are, independently of each other, hydrogen, alkyl, aralkyl, or a covalent bond attaching the ligand to a linker, or R^{25} and R^{26} together with the nitrogen atom to which they are attached form a heterocycloamino group which optionally attaches the ligand to a linker provided that at least one of the R^{24}, R^{25}, and R^{26} attaches the ligand to a linker; and

each ligand, L, that is an allosteric modulator of a muscarinic receptor in the multibinding compound of Formula (I) is independently selected from a group consisting of:

(7) a compound of formula (g):



(g)

wherein:

D" is alkylene;

D is $-NR^{31}R^{32}$, $-N^{+}(R^{33}R^{34}R^{35})$ or $-OR^{32}$ where R^{31}, R^{33}, and R^{34} are,

independently of each other, hydrogen, alkyl, or aralkyl; and R^{32} and R^{35} represent a covalent bond attaching the ligand to a linker;

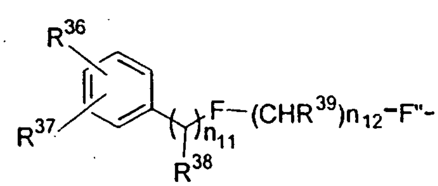
R^{27} is hydrogen, halo, nitro, cyano, hydroxy, alkoxy, carboxy, alkoxycarbonyl, acyl, thio, alkylthio, alkylsulfonyl, alkylsulfinyl, sulfonamido, alkylsulfonamido, carbamoyl, thiocarbamoyl, mono or dialkylcarbamoyl, amino, mono- or dialkylamino, aryl, aryloxy, arylthio, heteroaryl, heteraryloxy, heteroarylthio, heterocyclyl, heterocyclyloxy, aralkyl, heteroaralkyl, or alkyl optionally substituted with one, two or three substituents selected from halo, hydroxy, carboxy, alkoxycarbonyl, alkylthio, alkylsulfonyl, amino, or substituted amino;

R^{28} is hydrogen, halo, nitro, cyano, hydroxy, alkoxy, carboxy, alkoxycarbonyl, acyl, thio, alkylthio, alkylsulfonyl, alkylsulfinyl, sulfonamido, alkylsulfonamido, carbamoyl, thiocarbamoyl, mono or dialkylcarbamoyl, amino, mono- or dialkylamino, or alkyl optionally substituted with one, two, or three substituents selected from halo, hydroxy, carboxy, alkoxycarbonyl, alkylthio, alkylsulfonyl, amino, or substituted amino;

R^{29} and R^{30} are, independently of each other, hydrogen, alkyl, haloalkyl, halo, nitro, cyano, hydroxy, alkoxy, alkoxycarbonyl, acyl, thio, alkylthio, amino, mono- or dialkylamino; or

one of R^{27}, R^{28}, R^{29}, or R^{30} together with the adjacent group forms a methylenedioxy or ethylenedioxy group; or

(8) a compound of formula (h):



(h)

wherein:

n_{11} is an integer of from 1 to 7;

n_{12} is an integer of from 0 to 7;

F is $-NR^{40}-$, -O-, -S-, or $-CHR^{41}-$ (wherein R^{40} and R^{41} are, independently of each other, hydrogen or alkyl);

F" is a covalent bond, $-OR^{43}$, $-NR^{42}R^{43}$, or $-N^{+}R^{43}R^{44}R^{45}$ wherein R^{42} is hydrogen or alkyl, R^{44} and R^{45} are alkyl, and R^{43} is a covalent bond attaching the ligand to a linker;

R^{36} is hydrogen, halo, nitro, cyano, hydroxy, alkoxy, carboxy, alkoxycarbonyl, acyl, thio, alkylthio, alkylsulfonyl, alkylsulfinyl, sulfonamido, alkylsulfonamido, carbamoyl, thiocarbamoyl, mono or dialkylcarbamoyl, amino, mono- or dialkylamino, aryl, aryloxy, arylthio, heteroaryl, heteraryloxy, heteroarylthio, heterocyclyl, heterocyclyloxy, aralkyl, heteroaralkyl, or alkyl optionally substituted with one, two or three substituents selected from halo, hydroxy, carboxy, alkoxycarbonyl, alkylthio, alkylsulfonyl, amino, or substituted amino;

R^{37} is hydrogen, halo, nitro, cyano, hydroxy, alkoxy, alkoxycarbonyl, acyl, thio, alkylthio, amino, mono- or dialkylamino, aryl, aryloxy, arylthio, heteroaryl, heteraryloxy, heteroarylthio, heterocyclyl, heterocyclyloxy, aralkyl, heteroaralkyl, or alkyl optionally substituted with one, two or three substituents selected from halo, hydroxy, carboxy, alkoxycarbonyl, alkylthio, alkylsulfonyl, amino, or substituted amino; and

R^{38} is hydrogen, alkyl, halo, hydroxy, alkoxy, or a covalent bond attaching the ligand to a linker provided that at least one of R^{38} and R^{43} attaches the ligand to a linker; and

pharmaceutically acceptable salts, individual isomers, mixture of isomers, and prodrugs thereof provided that at least one of the ligands is a muscarinic receptor antagonist.

15. The pharmaceutical composition Claim 14 wherein each linker independently has the formula:

$$-X^{a}-Z-(Y^{a}-Z)_{m}-Y^{b}-Z-X^{a}-$$

wherein

m is an integer of from 0 to 20;

X^a at each separate occurrence is selected from the group consisting of -O-, -S-, -NR-, -C(O)-, -C(O)O-, -C(O)NR-, -C(S), -C(S)O-, -C(S)NR- or a covalent bond where R is as defined below;

Z is at each separate occurrence is selected from the group consisting of alkylene, substituted alkylene, cycloalkylene, substituted cylcoalkylene, alkenylene, substituted alkenylene, alkynylene, substituted alkynylene, cycloalkenylene, substituted cycloalkenylene, arylene, heteroarylene, heterocyclene, or a covalent bond;

Y^a and Y^b at each separate occurrence are selected from the group consisting of -O-, -C(O)-, -OC(O)-, -C(O)O-, -NR-, -S(O)n-, -C(O)NR'-, -NR' C(O)-, -NR' C(O)NR'-, -NR' C(S)NR'-, -C(=NR')-NR'-, -NR'-C(=NR')-, -OC(O)-NR'-, -NR'-C(O)-O-, -N=C(X^a)-NR'-, -NR'-C(X^a)=N-,-P(O)(OR')-O-, -O-P(O)(OR')-, -S($O)_n$CR' R"-, -S$(O)_n$-NR'-, -NR'-S$(O)_n$ -, -S-S-, and a covalent bond; where *n* is 0, 1 or 2; and R, R' and R" at each separate occurrence are selected from the group consisting of hydrogen, alkyl, substituted alkyl, cycloalkyl, substituted cycloalkyl, alkenyl, substituted alkenyl, cycloalkenyl, substituted cycloalkenyl, alkynyl, substituted alkynyl, aryl, heteroaryl, and heterocyclic.

16. A method for treating diseases mediated by a muscarinic receptor in a mammal, said method comprising administering to said mammal a therapeutically effective amount of a pharmaceutical composition comprising a pharmaceutically acceptable carrier and a multibinding compound comprising from 2 to 10 ligands covalently attached to one or more linkers, wherein each of said ligands, comprises, independently of each other, a muscarinic receptor antagonist or an allosteric modulator of a muscarinic receptor provided that at least one of said ligands is a muscarinic receptor antagonist, and pharmaceutically acceptable salts thereof.

17. A method for treating diseases mediated by a muscarinic receptor in a

mammal, said method comprising administering to said mammal a therapeutically effective amount of a pharmaceutical composition comprising a pharmaceutically acceptable carrier and a multibinding compound of Claim 9.

18. A method for treating diseases mediated by a muscarinic receptor in a mammal, said method comprising administering to said mammal a therapeutically effective amount of a pharmaceutical composition comprising a pharmaceutically acceptable carrier and a multibinding compound of Claim 11.

19. A method for identifying multimeric ligand compounds possessing multibinding properties for a muscarinic receptor which method comprises:

(a) identifying a ligand or a mixture of ligands wherein each ligand contains at least one reactive functionality;

(b) identifying a library of linkers wherein each linker in said library comprises at least two functional groups having complementary reactivity to at least one of the reactive functional groups of the ligand;

(c) preparing a multimeric ligand compound library by combining at least two stoichiometric equivalents of the ligand or mixture of ligands identified in (a) with the library of linkers identified in (b) under conditions wherein the complementary functional groups react to form a covalent linkage between said linker and at least two of said ligands; and

(d) assaying the multimeric ligand compounds produced in the library prepared in (c) above to identify multimeric ligand compounds possessing multibinding properties for a muscarinic receptor.

20. A method for identifying multimeric ligand compounds possessing multibinding properties for a muscarinic receptor which method comprises:

(a) identifying a library of ligands wherein each ligand contains at least one reactive functionality;

(b) identifying a linker or mixture of linkers wherein each linker

comprises at least two functional groups having complementary reactivity to at least one of the reactive functional groups of the ligand;

(c) preparing a multimeric ligand compound library by combining at least two stoichiometric equivalents of the library of ligands identified in (a) with the linker or mixture of linkers identified in (b) under conditions wherein the complementary functional groups react to form a covalent linkage between said linker and at least two of said ligands; and

(d) assaying the multimeric ligand compounds produced in the library prepared in (c) above to identify multimeric ligand compounds possessing multibinding properties for a muscarinic receptor.

21. The method according to Claim 19 or 20 wherein the preparation of the multimeric ligand compound library is achieved by either the sequential or concurrent combination of the two or more stoichiometric equivalents of the ligands identified in (a) with the linkers identified in (b).

22. The method according to Claim 21 wherein the multimeric ligand compounds comprising the multimeric ligand compound library are dimeric.

23. The method according to Claim 22 wherein the dimeric ligand compounds comprising the dimeric ligand compound library are heterodimeric.

24. The method according to Claim 23 wherein the heterodimeric ligand compound library is prepared by sequential addition of a first and second ligand.

25. The method according to Claim 19 or 20 wherein, prior to procedure (d), each member of the multimeric ligand compound library is isolated from the library.

26. The method according to Claim 25 wherein each member of the library is

isolated by preparative liquid chromatography mass spectrometry (LCMS).

27. The method according to Claim 19 or Claim 20 wherein the linker or linkers employed are selected from the group comprising flexible linkers, rigid linkers, hydrophobic linkers, hydrophilic linkers, linkers of different geometry, acidic linkers, basic linkers, linkers of different polarization and amphiphilic linkers.

28. The method according to Claim 27 wherein the linkers comprise linkers of different chain length and/or having different complementary reactive groups.

29. The method according to Claim 28 wherein the linkers are selected to have different linker lengths ranging from about 2 to 100Å.

30. The method according to Claim 19 or 20 wherein the ligand or mixture of ligands is selected to have reactive functionality at different sites on said ligands.

31. The method according to Claim 30 wherein said reactive functionality is selected from the group consisting of carboxylic acids, carboxylic acid halides, carboxyl esters, amines, halides, pseudohalides, isocyanates, vinyl unsaturation, ketones, aldehydes, thiols, alcohols, anhydrides, boronates, and precursors thereof wherein the reactive functionality on the ligand is selected to be complementary to at least one of the reactive groups on the linker so that a covalent linkage can be formed between the linker and the ligand.

32. The method according to Claim 19 or Claim 20 wherein the multimeric ligand compound library comprises homomeric ligand compounds.

33. The method according to Claim 19 or Claim 20 wherein the multimeric ligand compound library comprises heteromeric ligand compounds.

34. A library of multimeric ligand compounds which may possess multivalent properties for a muscarinic receptor which library is prepared by the method comprising:

(a) identifying a ligand or a mixture of ligands wherein each ligand contains at least one reactive functionality;

(b) identifying a library of linkers wherein each linker in said library comprises at least two functional groups having complementary reactivity to at least one of the reactive functional groups of the ligand; and

(c) preparing a multimeric ligand compound library by combining at least two stoichiometric equivalents of the ligand or mixture of ligands identified in (a) with the library of linkers identified in (b) under conditions wherein the complementary functional groups react to form a covalent linkage between said linker and at least two of said ligands.

35. A library of multimeric ligand compounds which may possess multivalent properties for a muscarinic receptor which library is prepared by the method comprising:

(a) identifying a library of ligands wherein each ligand contains at least one reactive functionality;

(b) identifying a linker or mixture of linkers wherein each linker comprises at least two functional groups having complementary reactivity to at least one of the reactive functional groups of the ligand; and

(c) preparing a multimeric ligand compound library by combining at least two stoichiometric equivalents of the library of ligands identified in (a) with the linker or mixture of linkers identified in (b) under conditions wherein the complementary functional groups react to form a covalent linkage between said linker and at least two of said ligands.

36. The library according to Claim 34 or Claim 35 wherein the linker or linkers employed are selected from the group comprising flexible linkers, rigid linkers,

hydrophobic linkers, hydrophilic linkers, linkers of different geometry, acidic linkers, basic linkers, linkers of different polarization and/or polarizability and amphiphilic linkers.

37. The library according to Claim 36 wherein the linkers comprise linkers of different chain length and/or having different complementary reactive groups.

38. The library according to Claim 37 wherein the linkers are selected to have different linker lengths ranging from about 2 to 100Å.

39. The library according to Claim 34 or 35 wherein the ligand or mixture of ligands is selected to have reactive functionality at different sites on said ligands.

40. The library according to Claim 39 wherein said reactive functionality is selected from the group consisting of carboxylic acids, carboxylic acid halides, carboxyl esters, amines, halides, pseudohalides, isocyanates, vinyl unsaturation, ketones, aldehydes, thiols, alcohols, anhydrides, boronates, and precursors thereof wherein the reactive functionality on the ligand is selected to be complementary to at least one of the reactive groups on the linker so that a covalent linkage can be formed between the linker and the ligand.

41. The library according to Claim 35 or Claim 36 wherein the multimeric ligand compound library comprises homomeric ligand compounds.

42. The library according to Claim 34 or Claim 35 wherein the multimeric ligand compound library comprises heteromeric ligand compounds.

43. An iterative method for identifying multimeric ligand compounds possessing multibinding properties for a muscarinic receptor which method comprises:

(a) preparing a first collection or iteration of multimeric compounds

which is prepared by contacting at least two stoichiometric equivalents of the ligand or mixture of ligands which target a receptor with a linker or mixture of linkers wherein said ligand or mixture of ligands comprises at least one reactive functionality and said linker or mixture of linkers comprises at least two functional groups having complementary reactivity to at least one of the reactive functional groups of the ligand wherein said contacting is conducted under conditions wherein the complementary functional groups react to form a covalent linkage between said linker and at least two of said ligands;

(b) assaying said first collection or iteration of multimeric compounds to assess which if any of said multimeric compounds possess multibinding properties for a muscarinic receptor;

(c) repeating the process of (a) and (b) above until at least one multimeric compound is found to possess multibinding properties for a muscarinic receptor;

(d) evaluating what molecular constraints imparted multibinding properties to the multimeric compound or compounds found in the first iteration recited in (a)- (c) above;

(e) creating a second collection or iteration of multimeric compounds which elaborates upon the particular molecular constraints imparting multibinding properties to the multimeric compound or compounds found in said first iteration;

(f) evaluating what molecular constraints imparted enhanced multibinding properties to the multimeric compound or compounds found in the second collection or iteration recited in (e) above;

(g) optionally repeating steps (e) and (f) to further elaborate upon said molecular constraints.

44. The method according to Claim 43 wherein steps (e) and (f) are repeated from 2-50 times.

45. The method according to Claim 44 wherein steps (e) and (f) are repeated from 5-50 times.

FIG. 1

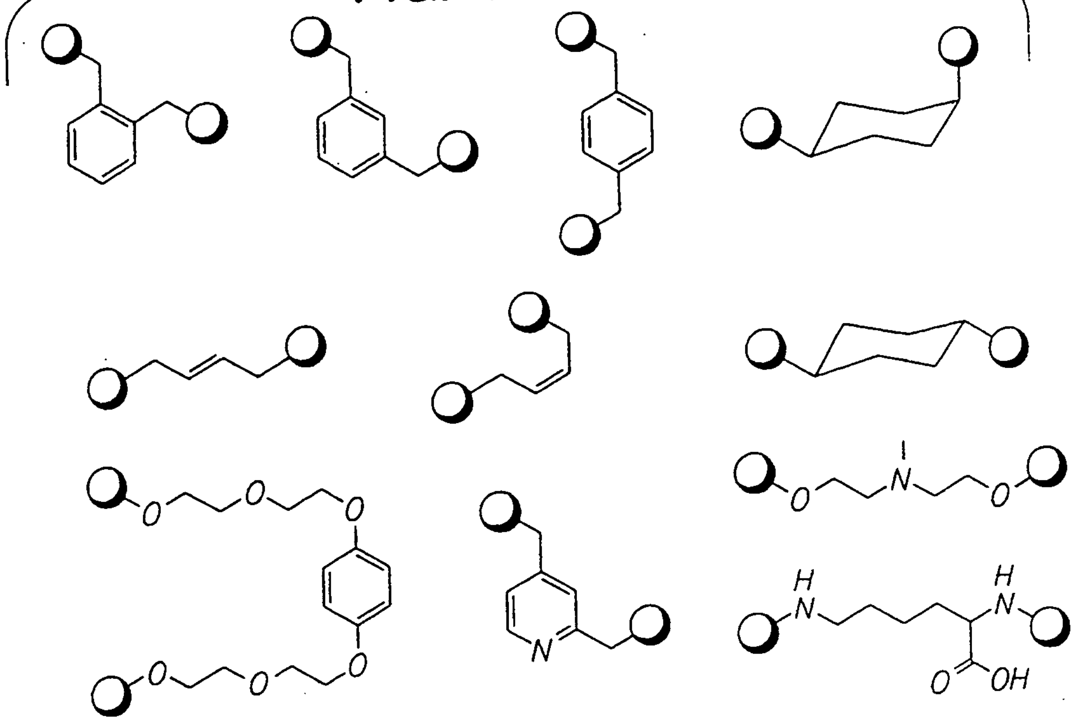


FIG. 2

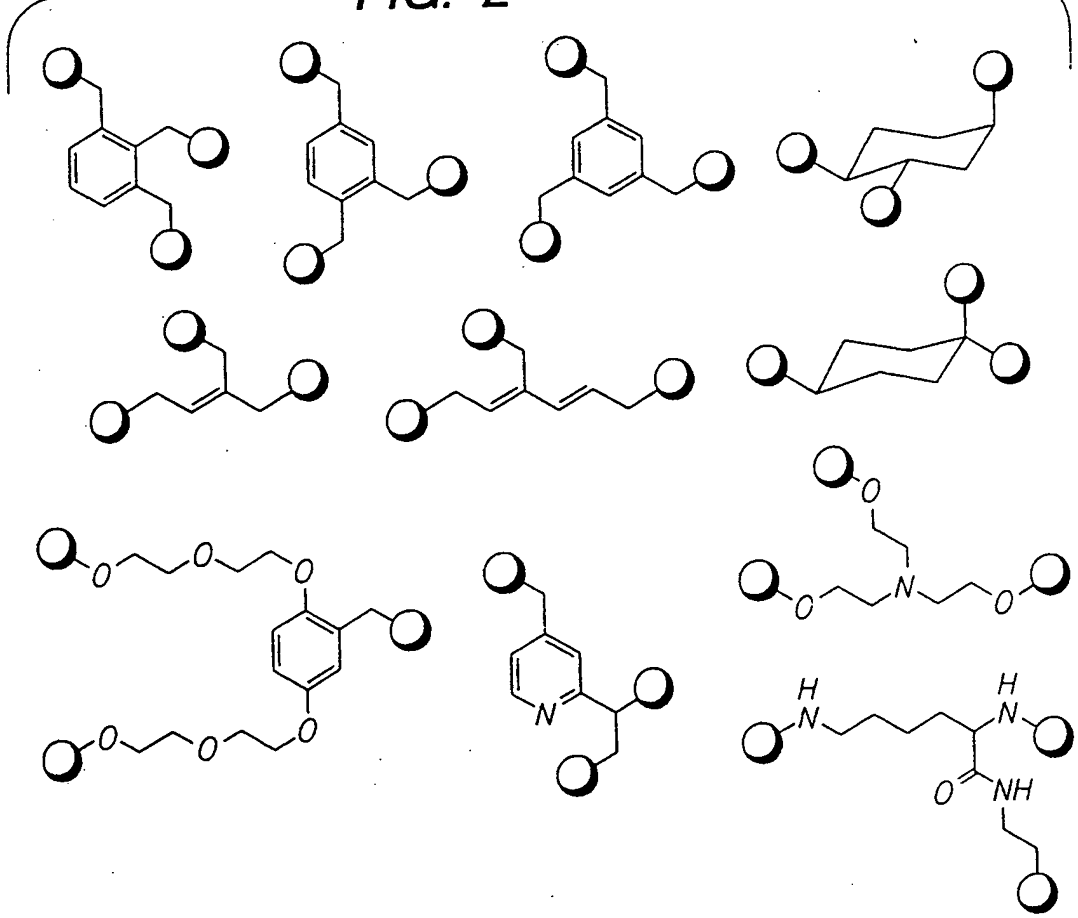


FIG. 4

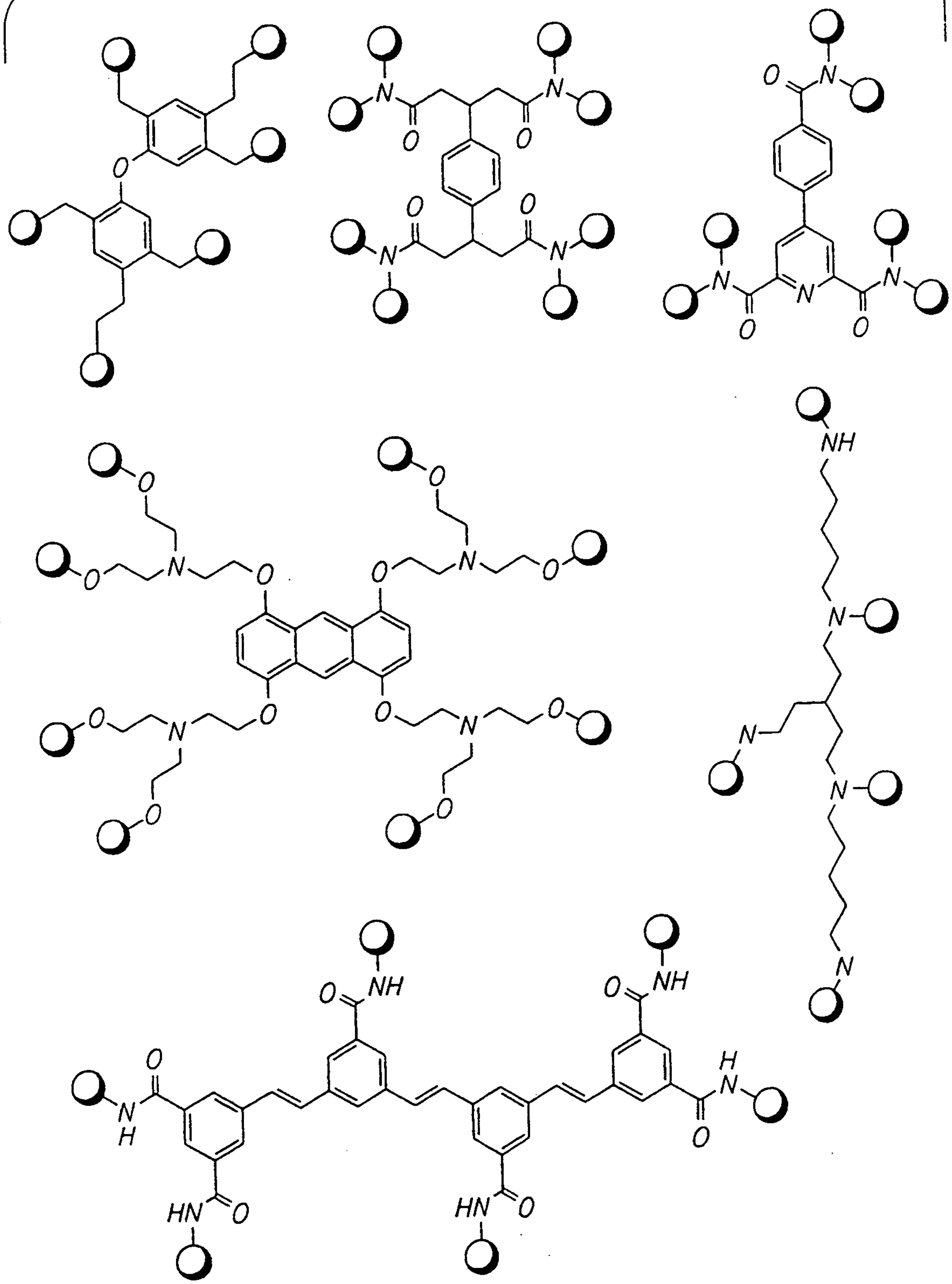
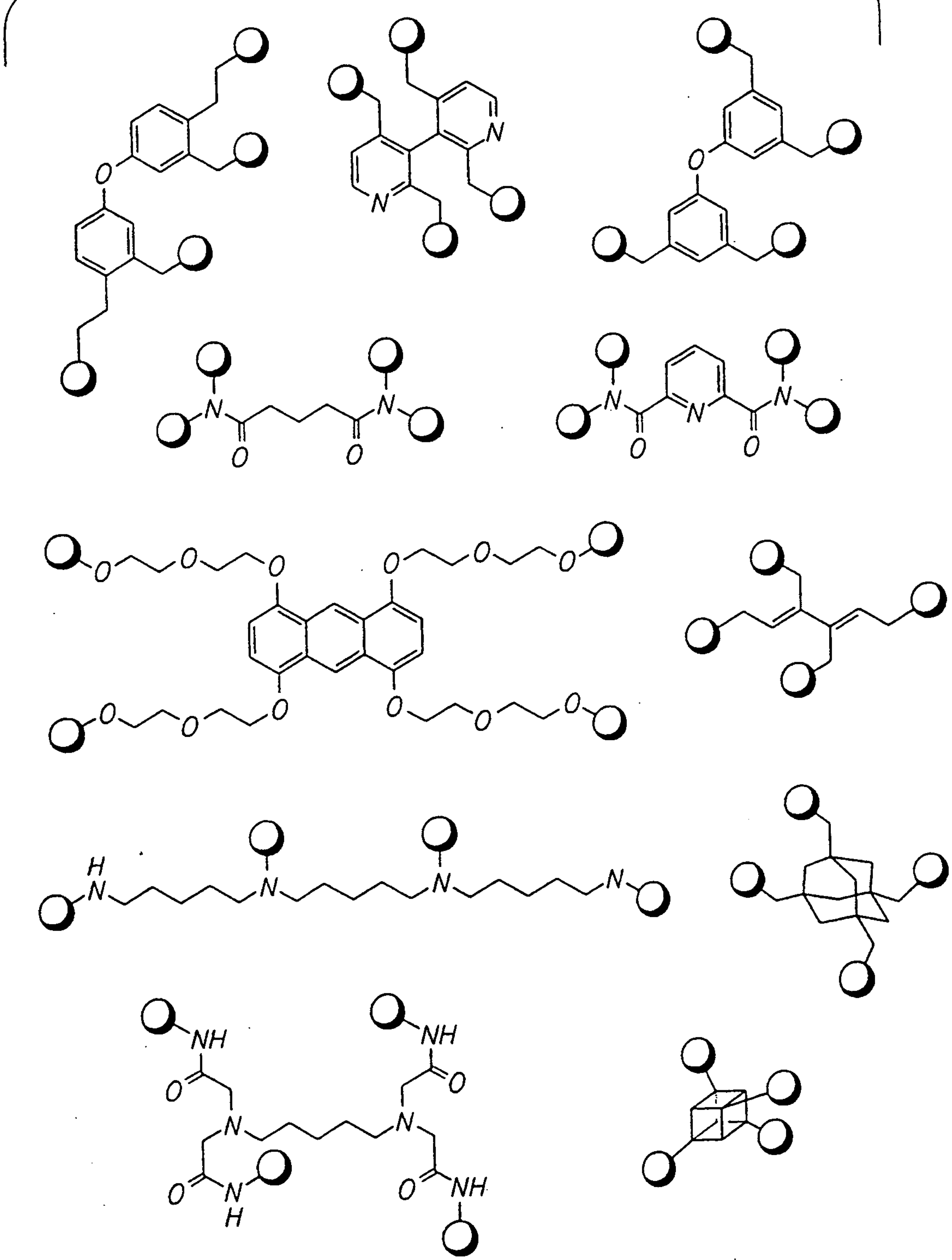


FIG. 3



INTERNATIONAL SEARCH REPORT

International application No.
PCT/US99/12733

A. CLASSIFICATION OF SUBJECT MATTER

IPC(6) :Please See Extra Sheet.
US CL :Please See Extra Sheet.

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 424/1.11, 9.1, 178.1, 193.1; 435/7.1, 7.2; 436/501, 518; 514/183, 186, 188; 530/345, 389.1, 401, 807

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

Please See Extra Sheet.

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	PIERGENTILI et al. Synthesis and Muscarinic Receptors Affinity of a Series of Antagonist Bivalent Ligands. Il Farmaco. 1994, Vol. 49, No. 2, pages 83-87, see entire article, especially Table 1.	1-45
Y	WO 92/05802 A1 (NEORX CORPORATION) 16 April 1992 (16/04/92), see Abstract, pages 3 lines 1-25, page 4 lines 20-27, page 5 lines 6-18, page 21 lines 4-33, page 22 lines 1-8 and claim 1.	1-45
Y	US 4,587,046 A (GOODMAN et al) 06 May 1986 (06/05/86), see entire document, especially columns 1-9.	1-45

[X] Further documents are listed in the continuation of Box C. [ ] See patent family annex.

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search

27 SEPTEMBER 1999

Date of mailing of the international search report

18 OCT 1999

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INTERNATIONAL SEARCH REPORT

International application No.
PCT/US99/12733

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	LEE et al. Alanine Scanning Mutagenesis of Conserved Arginine/Lysine-Arginine/Lysine-X-X-Arginine/Lysine G Protein-Activating Motifs on m1 Muscarinic Acetylcholine Receptors. Mol. Pharmacology. July 1996, Vol. 50, pages 140-148, see entire article, especially page 142.	19-45
Y	KAHNE, D. Combinatorial Approaches to Carbohydrates. Curr. Opin. Chem. Biol. June 1997, Vol. 1, No. 1, pages 130-135, see entire article.	19-45
Y	LIANG et al. Parallel Synthesis and Screening of a Solid Phase Carbohydrate Library. Science. 29 November 1996, Vol. 274, pages 1520-1522. see entire article.	19-45
Y	SHUKER et al. Discovering High-Affinity Ligands for Proteins: SAR by NMR. Science. 29 November 1996, Vol. 274, pages 1531-1534, see entire article, especially Figure 1.	19-45
Y	US 4,675,326 A (AMITAI et al) 23 June 1987 (23/06/87), see entire document, especially columns 1-4 and column 6.	1-18
Y	US 4,567,178 A (EBERLEIN et al) 28 January 1986 (28/01/86), see entire document.	1-18
Y	US 5,534,520 A (FISHER et al) 09 July 1996 (09/07/96), see entire document, especially Abstract, column 3 and Tables 1-5.	1-18

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US99/12733

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

Please See Extra Sheet.

1. ☒ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest
☐ The additional search fees were accompanied by the applicant's protest.
☒ No protest accompanied the payment of additional search fees.

A. CLASSIFICATION OF SUBJECT MATTER:
IPC (6):

A61K 38/00, 39/00, 39/44, 39/395, 51/00; A01N 43/00, 55/02; C07K 2/00, 4/00; G01N 33/53, 33/543, 33/566

A. CLASSIFICATION OF SUBJECT MATTER:
US CL :

424/1.11, 9.1, 178.1, 193.1; 435/7.1, 7.2; 436/501, 518; 514/183, 186, 188; 530/345, 389.1, 401, 807

B. FIELDS SEARCHED
Electronic data bases consulted (Name of data base and where practicable terms used):

APS, STN (REGISTRY, CAPLUS, BIOSIS, MEDLINE, SCISEARCH)
Search terms: Structure search, multivalent, multibinding, polyvalent, multimeric, combinatorial, library, ligand, link?, muscarinic, receptor

BOX II. OBSERVATIONS WHERE UNITY OF INVENTION WAS LACKING
This ISA found multiple inventions as follows:

This application contains the following inventions or groups of inventions which are not so linked as to form a single inventive concept under PCT Rule 13.1. In order for all inventions to be searched, the appropriate additional search fees must be paid.

Group I, claim(s) 1-18, drawn to multibinding compounds comprising a muscarinic receptor antagonist or allosteric modulator, pharmaceutical composition and method of treatment.
Group II, claim(s) 19-45, drawn to a method for identifying multimeric ligand compounds possessing multibinding properties for a muscarinic receptor, a multimeric ligand compound library and an iterative method for identifying multimeric ligand compounds possessing multibinding properties for a muscarinic receptor.

This application contains claims directed to more than one species of the generic invention. These species are deemed to lack Unity of Invention because they are not so linked as to form a single inventive concept under PCT Rule 13.1. In order for more than one species to be searched, the appropriate additional search fees must be paid. The species are as follows:

In Group I the species are as follows:
One species from Species Group A and one from Species Group B should be selected
Species Group A: The 8 ligands listed in claim 1.
Species Group B: The ligands labeled a-h listed in claims 4-5.

The claims are deemed to correspond to the species listed above in the following manner:

In Group I the species are as follows:
One species from Species Group A and one from Species Group B should be selected
Species Group A: The 8 ligands listed in claim 1.
Species Group B: The ligands labeled a-h listed in claims 4-5.
Claims 4 and 9 correspond to ligands a-f
Claim 5 corresponds to ligands g and h

The following claims are generic: 1-3, 6-8 and 10-18.

The inventions listed as Groups I-II do not relate to a single inventive concept under PCT Rule 13.1 because, under PCT Rule 13.2, they lack the same or corresponding special technical features for the following reasons:

The two groups do not share a special technical feature. The technical feature that links the claims of Group I is the multibinding compounds of specific structures which comprise a muscarinic receptor antagonist or an allosteric modulator of a muscarinic receptor. The technical feature that links the claims of Group II is the multimeric ligand compound library possessing multibinding properties for a muscarinic receptor. These technical features represent

different inventive concepts and there fore the groups lack unity.

The species listed above do not relate to a single inventive concept under PCT Rule 13.1 because, under PCT Rule 13.2, the species lack the same or corresponding special technical features for the following reasons:

PCT Rule 13.2 states that unity of invention shall be fulfilled when there is a technical relationship among those inventions involving one or more of the same or corresponding special technical features". It further defines "special technical feature" as "those technical features that define a contribution which each of the claimed inventions, claimed as a whole, makes over the prior art". For example, unity of invention is fulfilled if:
(a) all alternatives have a common property; and
(b) (i) a common structure is present, i. e. a significant structural element is shared by all alternatives, or
(b) (ii) in cases where the common structure can not be the unifying criterion, all alternatives belong to a recognized class of compounds in the art to which the invention pertains. (MPEP Section 1850).

In the instant case, part (a) above is not fulfilled because all claimed species of ligand do not have a common property. Furthermore, the compounds encompassed by the instant formulas do not all possess a common structure (no shared significant structural element)and do not belong to a recognized class of compounds in the art to which they pertain. For the forgoing reasons, election under these rules is proper and required.

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